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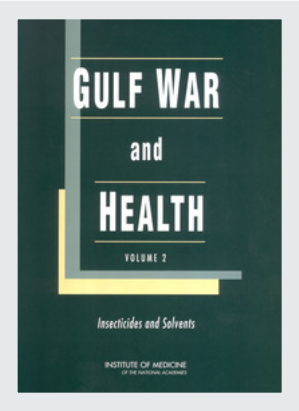

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Gulf War and Health

Volume 2
Insecticides and Solvents

Committee on Gulf War and Health:
Literature Review of Pesticides and Solvents

Board on Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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COMMITTEE ON GULF WAR AND HEALTH: LITERATURE REVIEW OF PESTICIDES AND SOLVENTS

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REVIEWERS

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **DONALD R. MATTISON**, Senior Adviser, National Institute of Child Health and Human Development and the Center for Research for Mothers and Children, who was appointed by the Institute of Medicine and **HAROLD C. SOX**, *Annals of Internal Medicine*, American College of Physicians–American Society of Internal Medicine, who was appointed by the Report Review Committee. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the institution.

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PREFACE

More than a decade has passed since the Gulf War. After the Iraqi invasion of Kuwait on August 2, 1990, about 700,000 US military personnel were deployed to the Persian Gulf. Air attacks against Iraqi forces began on January 2, 1991, and the ground war followed between February 24 and 28. Despite the short duration and the small number of immediate casualties, allied forces were exposed to the horrors of war and to many noxious substances. After the war, large numbers of veterans suffered from a variety of symptoms characterized in part by fatigue, headache, difficulties of cognition, and vague arthralgias. Studies of military personnel clearly demonstrate that the prevalence of those symptoms has been higher in those deployed to the Persian Gulf than in those not deployed.

Veterans, Congress, the Department of Defense (DOD), and the Department of Veterans Affairs (VA) all have been deeply concerned about the etiology of the symptoms that were so prevalent among Gulf War veterans. As a result of requests by Congress, the Institute of Medicine (IOM) has embarked on a series of studies to review the health effects of many of the biologic, chemical, and environmental agents to which veterans may have been exposed. Our committee was charged in the second study to review the literature on the long-term human health effects of insecticides and solvents thought to have been used in the Gulf War.

Because of the large volume of literature on those compounds, IOM appointed a 37-member committee, one of the largest committees in its history. Our committee is composed of epidemiologists, toxicologists, industrial hygienists, and physicians with expertise in a number of relevant fields, including occupational medicine, neurology, dermatology, oncology, family medicine, and internal medicine.

The task of this committee was to identify for review the literature that focused on the insecticides and solvents to which Gulf War veterans may have been exposed. DOD, VA, RAND researchers, and Gulf War veterans provided information about the agents used.

The committee addressed the full scope of health effects that are potentially associated with insecticides and solvents, not just the veterans' symptoms. It focused on human studies of long-term effects that might follow exposure to those agents, inasmuch as veterans' symptoms have continued long after the war. The primary literature reviewed was epidemiologic studies of various occupational groups; when available, studies of Gulf War veterans were included in the committee's analysis. Experimental data and toxicologic studies provided information about the acute and long-term effects of insecticides and solvents on humans and animals and about plausible biologic mechanisms of adverse health outcomes.

The committee placed its conclusions in categories of strength of evidence. Similar categories were used in Volume 1 of *Gulf War and Health* and in numerous other IOM studies.

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Given the varied expertise and judgment within the committee, members occasionally differed in their interpretation of findings. In some instances committee members, even after careful deliberation, could not reach consensus on the category of association for a particular conclusion. In those instances, the committee presents no conclusion but discusses both points of view in the chapter and notes where additional research might be needed to draw more definitive conclusions.

Although the committee found associations between exposure to insecticides or solvents and some diseases and symptoms in some occupational groups, it was faced with a paucity of data regarding exposure for veterans. Therefore, it could not extrapolate from findings in published studies to the likelihood that veterans' illnesses are related to exposure to insecticides or solvents.

Despite the many challenges faced by the committee as it reviewed the epidemiologic literature, it arrived at numerous conclusions regarding associations. We hope that our review will be helpful not only for veterans but also for other groups interested in the long-term health outcomes of exposure to insecticides and solvents.

Jack M. Colwill, M.D., *Chair*

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The committee wishes to express its appreciation to the many people who contributed to this study by sharing their experience and providing their expertise. A number of Gulf War veterans presented information on the use of pesticides and solvents during the Gulf War. Speakers at the committee's May 2001 meeting included Venus Hammack, Desert Storm Battle Registry; Patrick Eddington, National Gulf War Resource Center; Kirt Love, Desert Storm Battle Registry; Denise Nichols, National Vietnam and Gulf War Veterans Coalition; Ed Bryan, Persian Gulf Era Veterans, Massachusetts; and David Johnson, University of Oklahoma Health Sciences Center. In addition, the committee appreciates the information received from many other Gulf War veterans and their family members. The committee acknowledges the efforts of Department of Defense and Department of Veterans Affairs staff who provided background materials. The committee benefited greatly from the scientific expertise provided by reviewers and colleagues consulted in the course of the study including Neil Miller, Patricia Stewart, and David Zee. The committee values the contributions made by a number of individual consultants including—Miriam Davis, Diane Mundt, Mary Paxton, Elizabeth Tonkin, Marie-France Valois, and Lisa Zimmerman, and the assistance of Applied Epidemiology, Inc., of Amherst, Massachusetts. The committee also appreciates the support of the sponsor, the Department of Veterans Affairs.

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EXECUTIVE SUMMARY

The Gulf War was considered a brief and successful military operation, with few injuries and deaths of US troops. The war began in August 1990, and the last US ground troops returned home by June 1991. Although most Gulf War veterans resumed their normal activities, many began reporting a variety of unexplained health problems that they attributed to their participation in the Gulf War, including chronic fatigue, muscle and joint pain, loss of concentration, forgetfulness, headache, and rash.

One response to concerns about the veterans' health problems was a request by the Department of Veterans Affairs (VA) that the Institute of Medicine (IOM) review the scientific and medical literature on the long-term adverse health effects of agents to which the Gulf War veterans may have been exposed. In 1998, IOM and VA entered into a contract for a series of studies that would provide conclusions about the strength of associations between exposure to the agents of concern and health outcomes as observed in the epidemiologic literature.

Congress, also responding to the growing concerns of ill veterans, passed legislation in 1998 (the Persian Gulf War Veterans Act, PL 105–277, and the Veterans Programs Enhancement Act, PL 105–368) for a study similar to that previously requested by VA. The legislation directed the secretary of veterans affairs to enter into an agreement with IOM to review the literature on 33 agents believed to be associated with service in the Gulf War and to assess the strength of the evidence of associations between exposure to the agents and long-term adverse health effects. The legislation directed the secretary to consider the IOM conclusions when making decisions about compensation.

The following agents are listed in PL 105–277 and PL 105–368:

Pesticides: organophosphorous pesticides (chlorpyrifos, diazinon, dichlorvos, and malathion), carbamate pesticides (proxpur[1], carbaryl, and methomyl), and chlorinated-hydrocarbons and other pesticides and repellents (lindane, pyrethrins, permethrins[2], rodenticides [bait], and the repellent DEET [*N,N*-diethyl-3-methylbenzamide])

Pyridostigmine bromide

Nerve agents and precursor compounds: sarin and tabun

Synthetic chemical compounds: mustard agents, volatile organic compounds, hydrazine, red fuming nitric acid, and solvents

Environmental particles and pollutants: hydrogen sulfide, oil-fire byproducts, diesel heater fumes, and sand microparticles

[1] The committee searched and examined the literature on the insecticide propoxur.

[2] Permethrin is the name of a specific pyrethroid insecticide.

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Sources of radiation: uranium, depleted uranium, microwave radiation, and radiofrequency radiation
Diseases endemic to the region: leishmaniasis, sandfly fever, pathogenic *Escherichia coli*, and shigellosis
Administration of live, "attenuated," and toxoid vaccines.

In response to VA and Congress, IOM determined that the study would be conducted in phases and that the initial phase would include a review of the agents that were of most concern to the veterans. After meetings with Gulf War veterans, the first IOM Gulf War committee decided that its study would focus on depleted uranium, pyridostigmine bromide, sarin, and vaccines (anthrax and botulinum toxoid).

After reviewing IOM's *Gulf War and Health, Volume 1,* the secretary of veterans affairs determined that there was no basis to establish a presumption of a connection between Gulf War exposure to sarin, pyridostigmine bromide, depleted uranium, or anthrax or botulinum toxoid vaccine and various health outcomes.

SCOPE OF VOLUME 2

This second volume focuses on long-term adverse health outcomes associated with exposure to insecticides and solvents. The IOM committee that was formed to conduct the second study began its work by overseeing extensive searches of the peer-reviewed medical and scientific literature. The searches retrieved about 30,000 potentially relevant references which were considered by the committee and staff. After an assessment of the references, the committee focused on about 3000 that analyzed the relevant insecticides and solvents and their long-term adverse health effects in humans. The committee did not review the literature on short-term outcomes, inasmuch as the veterans, their families, VA, and Congress are concerned with health effects that might persist long after exposure ceased and that might require compensation.

It should be noted that the charge to IOM was not to determine whether a unique Gulf War syndrome exists or to judge whether veterans were exposed to the putative agents. Nor was the charge to focus on broader issues, such as the potential costs of compensation for veterans or policy regarding such compensation; that policy is the responsibility of the secretary of veterans affairs. The committee's charge was to assess the scientific evidence regarding long-term health effects associated with exposure to specific agents that were potentially present during the Gulf War. Epidemiologic studies that analyzed the relationship between exposure to specific chemicals under review and long-term health outcomes provided the evidence for the committee to use in drawing conclusions of association.

METHODS

As the committee began its task, the first step was to broadly identify the literature for review. Searches were conducted by using the names and synonyms of the specific insecticides and solvents identified for study, their Chemical Abstract Service registry numbers, and the relevant classes of insecticides and solvents. Searches were also conducted on occupations with known exposure to insecticides or solvents (such as pesticide application, painting, and dry

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cleaning). Finally, background documents and reviews of experimental evidence were retrieved and examined.

The literature search resulted in the retrieval of about 30,000 titles. As the titles and abstracts were reviewed, it became apparent that many of the studies were not relevant to the committee's task. The committee therefore developed inclusion criteria for the studies to be reviewed; for example, there had to be an examination of the agents under consideration, the study design had to be appropriate for the committee's task of weighing evidence, and the publication had to be an original study rather than a review or meta-analysis. Results of the studies also had to demonstrate persistent rather than short-term effects. Applying those criteria helped the committee to narrow the 30,000 titles and abstracts to about 3000 peer-reviewed studies that were carefully reviewed. The studies were primarily occupational studies of workers exposed chronically to insecticides or solvents, including studies of Gulf War veterans that specifically examined insecticide and solvent exposure. Examples of studies excluded from review were those which focused solely on the efficacy of insecticide use in mitigating the effects of insect infestation or examined pesticide ingestion and suicide. Similarly, studies of occupations with exposure to multiple agents and those without specificity of agent (for example, farming and agricultural work) were excluded in that it was difficult to determine the agent responsible for an outcome. Case studies of acute poisonings or short-term outcomes were also excluded.

It should be noted that animal studies had a limited role in the committee's assessment of association between exposure and health outcome. Animal data were used for making assessments of biologic plausibility; they were not used as part of the weight-of-evidence approach to determining likelihood that an exposure to a specific agent might have a specific long-term outcome. The animal studies were, however, used as evidence to support the epidemiologic data.

The committee did not collect original data or perform secondary data analysis. It did, however, calculate confidence intervals, when a study did not provide them, on the basis of the number of subjects (cases and controls), the relative risk or odds ratio, or the *p* value.

DRAWING CONCLUSIONS ABOUT THE LITERATURE

As noted, the committee adopted a policy of using only published, peer-reviewed literature to draw its conclusions. Although the process of peer review by fellow professionals enhances the likelihood that a study has reached valid conclusions, it does not guarantee validity. Accordingly, committee members read each study and considered its relevance and quality.

The committee classified the evidence of association between exposure to a specific agent and a specific health outcome into five previously established categories, as set forth below. The categories closely resemble those used by several IOM committees that have evaluated vaccine safety, herbicides used in Vietnam, and indoor pollutants related to asthma. The first three categories imply a statistical association. The committee's conclusions are based on the strength and coherence of the findings in the available studies. The conclusions represent the committee's collective judgment. The committee endeavored to express its judgment as clearly and precisely as the available data allowed. It used the established categories of association from previous IOM studies because they have gained wide acceptance over more than a decade by Congress, government agencies, researchers, and veterans groups.

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However, inasmuch as each committee member relied on his or her training, expertise, and judgment, the committee's conclusions have both quantitative and qualitative aspects. In some cases, committee members were unable to agree on the strength of evidence of an association under review; in such instances, if a consensus conclusion could not be reached, the committee presented their different points of view in the text.

The five categories describe different levels of association and sound a recurring theme: the validity of an association is likely to vary with the extent to which the authors reduced common sources of error in making inferences—chance variation, bias, and confounding. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced. The five categories and their rationale are as follows.

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, biologic plausiblility, and a temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance[3] and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality[4] study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively,

[3]Chance refers to sampling variability.

[4]Factors used to characterize high quality studies include, the statistical stability of the associations, whether dose–response or other trends were demonstrated, whether the association was among numerous comparisons that were made, and the quality of the assessments of exposure and outcome. Specifically, the quality of exposure assessment refers to specificity and sensitivity in relation to the association of interest. For instance, for insecticides, studies assessing specific insecticides (such as chlorpyrifos) have more specificity than those assessing classes of insecticides (such as organophosphorous), which in turn are more specific than those assessing pesticides more generally. With respect to sensitivity, studies are judged by the instruments used to measure exposure. Biologic monitoring data are theoretically the most preferable but are almost never obtainable in the context of a nonpersistent chemical and a disease with long latency, like cancer. Other kinds of efforts can obtain sensitive measures of exposure, such as use of occupational or environmental monitoring data, use of more extensive industrial hygiene assessments, use of interview techniques that help to minimize recall bias (for example, photos of products, and home and workplace walkthroughs). Similarly, there are questions about quality of outcome assessment–whether an outcome has been verified by a medical diagnosis in a consistent fashion.

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several studies of less quality show consistent positive associations, and the results are probably not[5] due to bias, including confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from well-conducted studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

As the committee began its evaluation, neither the existence nor the absence of an association was presumed. Rather, the committee weighed the strengths and weaknesses of the available evidence to reach conclusions in a common format. It should be noted that although causation and association are often used synonymously, the committee distinguishes between "sufficient evidence of a causal relationship" and "sufficient evidence of an association." An association can indicate an increase in risk without the agent(s) being the sole or even primary cause.

Epidemiologic studies can establish statistical associations between exposure to specific agents and specific health effects, and associations are generally estimated by using relative risks or odds ratios. To conclude that an association exists, it is necessary for an agent to occur with the health outcome more frequently than expected by chance and it is almost always necessary to find that the effect occurs consistently in several studies. Epidemiologists seldom consider one study taken alone as sufficient to establish an association; rather, it is desirable to replicate the findings in other studies for conclusions to be drawn about the association. Results from separate studies are sometimes conflicting. It is sometimes possible to attribute discordant study results to such characteristics as the soundness of study design, the quality of execution, and the influence of different forms of bias. Studies that result in a statistically significant measure of association account for the role of chance in producing the observed result. When the measure of association does not show a statistically significant effect, it is important to consider the size of the sample and whether the study had the power to detect an effect if it existed.

Study designs differ in their ability to provide valid estimates of an association. Randomized controlled trials yield the most robust type of evidence, whereas cohort or case–control studies are more susceptible to bias. Cross-sectional studies, in general, provide a lower level of evidence than cohort and case–control studies. Determining whether a given statistical association rises to the level of causation requires inference. To assess explanations other than causality, one must bring together evidence from different studies and apply well-established criteria that have been refined over more than a century. Thus, by examining numerous epidemiologic studies, the committee addresses the question, "Does the available evidence support a causal relationship or an association between a particular exposure and a specific

[5]Factors used to make this judgment include the data on the relationship between potential confounders and related health end points in a given study, information on subject selection, and classification of exposure.

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health outcome?" An association between a specific agent and a specific health outcome does not mean that exposure to the agent invariably results in the health outcome or that all cases of the health outcome are the result of exposure to the agent. Such complete correspondence between exposure and disease is the exception in the study of disease in large populations. The committee evaluated the data and based its conclusions on the strength and coherence of the data in the selected studies. The committee's final conclusions represent its collective judgment; each committee member presented and discussed conclusions with the entire committee. In some cases committee members strongly believed that the literature supported, for example, a conclusion of "limited/suggested evidence of an association" when other members, on examination of the data, might have concluded that the evidence was "inadequate/insufficient of an association." In those instances, if a consensus conclusion could not be reached, opposing points of view are presented, and the committee notes that further research is needed to resolve the uncertainty.

Although the committee focused primarily on epidemiologic studies when drawing conclusions, there is a limited role for experimental evidence. Many of the chemicals that are examined in this report have been extensively studied in animals. A complete summary of all the available data on all the solvents and insecticides under review would fill many volumes. Given the small role of experimental studies in this report in the categorization of evidence, such a detailed review would serve no purpose. Instead, the report provides only a broad picture of the most important experimental toxicity data available in reliable secondary sources. For conclusions of "sufficient evidence of a causal relationship," the relevant experimental data are discussed where such a characterization is supported.

CONCLUSIONS

The following is a summary of the committee's conclusions on health outcomes associated with exposure to specific insecticides and solvents. If the entire committee did not agree on a conclusion, then the association was not assigned a category. It so happens that in each instance (listed below), the committee could not reach consensus on whether the association was limited/suggestive or inadequate/insufficient. The issues associated with the non-consensus associations are discussed in the text.

Consensus Not Reached on Category of Association

- Tetrachloroethylene and dry-cleaning solvents and esophageal cancer
- Trichloroethylene and colon cancer
- Mixtures of benzene, toluene, and xylene and colon cancer
- Tetrachloroethylene and dry-cleaning solvents and lung cancer
- Trichloroethylene and cervical cancer
- Solvents and kidney cancer.
- Benzene and solvents and brain and other central nervous system cancers
- Parental preconception exposure to solvents and childhood leukemia
- Organophosphorous insecticide exposure without OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

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Summary of the Committee's Consensus Conclusions

(These conclusions pertain to the particular insecticides and solvents identified as having been shipped to the Persian Gulf.)

SUFFICIENT EVIDENCE OF A CAUSAL RELATIONSHIP

Cancer And Other Health Outcomes:

- Benzene and acute leukemia
- Benzene and aplastic anemia

SUFFICIENT EVIDENCE OF AN ASSOCIATION

Cancer And Other Health Outcomes:

- Benzene and adult leukemia
- Solvents and acute leukemia
- Propylene glycol and allergic contact dermatitis

LIMITED/SUGGESTIVE EVIDENCE OF AN ASSOCIATION

Cancers:

- Tetrachloroethylene and dry-cleaning solvents and bladder cancer
- Solvents and bladder cancer
- Tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Organophosphorous insecticides and non-Hodgkin's lymphoma
- Carbamates and non-Hodgkin's lymphoma
- Benzene and non-Hodgkin's lymphoma
- Solvents and multiple myeloma
- Organophosphorous insecticides and adult leukemia
- Solvents and adult leukemia
- Solvents and myelodysplastic syndromes

Neurologic Effects:

- Organophosphorous insecticide exposure with OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)
- Solvents and neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

Other Health Effects:

- Solvents and reactive airways dysfunction syndrome (RADS) which would be evident with exposure and could persist for months or years
- Solvents and hepatic steatosis
- Solvents and chronic glomerulonephritis
- Insecticides and allergic contact dermatitis

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INADEQUATE/INSUFFICIENT EVIDENCE TO DETERMINE WHETHER AN ASSOCIATION EXISTS:

Cancers:

- Solvents and oral, nasal, or laryngeal cancer
- Insecticides and pancreatic cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and esophageal cancer
- Solvents and stomach, rectal, or pancreatic cancer
- Solvents other than trichloroethylene and mixtures of benzene, toluene, and xylene and colon cancer
- Insecticides and solvents and hepatobiliary cancers
- Insecticides and lung cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and lung cancer
- Solvents and bone cancer
- Solvents and melanoma or nonmelanoma skin cancer
- Insecticides and soft tissue sarcomas
- Lindane and solvents and breast cancer
- Solvents other than trichloroethylene and cervical cancer
- Solvents and ovarian or uterine cancer
- Solvents and prostate cancer
- Insecticides and prostate, testicular, bladder, or kidney cancers
- Specific solvents other than tetrachloroethylene and dry-cleaning solvents and bladder cancer
- Specific solvents other than tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Insecticides and brain and other central nervous system cancers
- Specific solvents other than benzene and brain and other central nervous system cancers
- Specific solvents other than benzene and non-Hodgkin's lymphoma
- Insecticides and solvents and Hodgkin's disease
- Insecticides and specific solvents and multiple myeloma
- Specific solvents other than benzene and acute and adult leukemia
- Benzene and myelodysplastic syndromes
- Parental preconception exposure to insecticides and childhood leukemias, brain and other central nervous system cancers, and non-Hodgkin's lymphoma
- Parental preconception exposure to solvents and neuroblastoma and childhood brain cancers

Neurologic Effects:

- Insecticides and solvents and peripheral neuropathy
- Insecticides and solvents and Parkinson's disease
- Insecticides and solvents and amyotrophic lateral sclerosis

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- Insecticides and solvents and Alzheimer's disease
- Solvents and multiple sclerosis
- Solvents and a long-term reduction in color discrimination
- Solvents and long-term hearing loss
- Solvents and long-term reduction in olfactory function

Reproductive Effects:

- Insecticides and solvents and male or female infertility after cessation of exposure
- Parental preconception exposure to insecticides or solvents and spontaneous abortion or other adverse pregnancy outcomes
- Parental preconception exposure to insecticides or solvents and congenital malformations

Other Health Effects:

- Insecticides and aplastic anemia
- Solvents other than benzene and aplastic anemia
- Insecticides and solvents and irreversible cardiovascular outcomes
- Insecticides and solvents and persistent respiratory symptoms or impairment after cessation of exposure
- Solvents and cirrhosis
- Solvents and alterations in liver function tests after cessation of exposure
- Solvents and chronic pancreatitis and other persistent gastrointestinal outcomes
- Solvents and the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus

LIMITED/SUGGESTIVE EVIDENCE OF NO ASSOCIATION

- No findings

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1

INTRODUCTION

The Gulf War was considered a brief and successful military operation, with few injuries and deaths of US troops. The war began in August 1990, and the last US ground troops returned home by June 1991. Although most Gulf War veterans resumed their normal activities, many soon began reporting a variety of unexplained health problems that they attributed to their participation in the Gulf War, including chronic fatigue, muscle and joint pain, loss of concentration, forgetfulness, headache, and rash (see Appendix A).

One response to concerns about the veterans' health problems was a request by the Department of Veterans Affairs (VA) that the Institute of Medicine (IOM) review the scientific and medical literature on the long-term adverse health effects of agents to which the Gulf War veterans may have been exposed. In 1998, the IOM and the VA entered into a contract for a series of studies that would provide conclusions about the strength of the association between exposure to the agents of concern and health outcomes as observed in the epidemiologic literature.

Congress, also responding to the growing concerns of ill veterans, passed legislation in 1998[1] for a similar study to that previously requested by the VA. The legislation directed the secretary of veterans affairs to enter into an agreement with IOM to review the literature on 33 agents related to service in the Gulf War and to assess the strength of associations between exposure to those agents and long-term adverse health effects as noted in the published literature. The legislation directs the secretary to consider the IOM conclusions when making decisions about compensation.

The following agents are listed in PL 105–277 and PL 105–368:

Pyridostigmine bromide.

Nerve agents and precursor compounds: Sarin and tabun.

Pesticides: Organophosphorous pesticides (chlorpyrifos, diazinon, dichlorvos, and malathion), carbamate pesticides (proxpur[2], carbaryl, and methomyl), and chlorinated-hydrocarbon and other pesticides and repellents (lindane, pyrethrins, permethrins[3], rodenticides [bait], and the repellent DEET [*N,N*-diethyl-3-methylbenzamide]).

Synthetic chemical compounds: Mustard agents, volatile organic compounds, hydrazine, red fuming nitric acid, and solvents.

Environmental particles and pollutants: Hydrogen sulfide, oil-fire byproducts, diesel heater fumes, and sand microparticles.

Sources of radiation: Uranium, depleted uranium, microwave radiation, and radiofrequency radiation.

[1]The two laws passed by Congress are the Persian Gulf War Veterans Act of 1998, PL 105–277, and the Veterans Programs Enhancement Act of 1998, PL 105–368.

[2] The committee searched and examined the literature on the insecticide propoxur.

[3] Permethrin is the name of a specific pyrethroid insecticide.

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Diseases endemic to the region: Leishmaniasis, sandfly fever, pathogenic *Escherichia coli*, and shigellosis.

Administration of live, "attenuated," and toxoid vaccines.

In response to VA and Congress, IOM determined that the study would be conducted in phases and that the initial phase would include review of the agents that were of most concern to the veterans. After meetings with Gulf War veterans, the first IOM Gulf War committee (*The Committee on Health Effects Associated with Exposure During the Gulf War*) decided that its study would focus on depleted uranium, pyridostigmine bromide, sarin, and vaccines (anthrax and botulinum toxoid).

After reviewing IOM's *Gulf War and Health, Volume I* (IOM, 2000) the secretary of veterans affairs determined that there was no basis to establish a presumption of a connection between Gulf War exposure to sarin, pyridostigmine bromide, depleted uranium, or anthrax and botulinum toxoid vaccines and various health outcomes (Department of Veterans Affairs, 2001). The conclusions and recommendations from the first report are presented in Appendix B.

SCOPE OF VOLUME 2

This second volume focuses on long-term adverse health outcomes associated with exposure to insecticides and solvents. The IOM committee that was formed to conduct the second study (*Gulf War and Health: Literature Review of Pesticides and Solvents*) began its work by overseeing extensive searches of the peer-reviewed medical and scientific literature, described in Appendix C and Chapter 2. The searches retrieved about 30,000 potentially relevant references that were considered by the committee and staff. All searches were completed by August 2001; relevant studies published after that date will be reviewed by future IOM committees. After an assessment of those references, the committee focused on approximately 3000 epidemiologic studies that analyzed associations between the relevant insecticides and solvents and long-term adverse health effects in humans.

Although the committee also examined the experimental evidence, animal studies had a limited role in its assessment of association between exposure and health outcome. The animal data were used to make assessments of biologic plausibility for adverse health outcomes. The animal data were not used as part of the weight-of-evidence to determine the likelihood that an exposure to a specific agent might cause a long-term outcome. The animal studies, however, were used as evidence to support the human epidemiologic data.

Information on the specific insecticides and solvents used during the Gulf War was obtained from a variety of sources, including veterans, the Department of Defense (DOD), VA, the RAND Corporation, the Presidential Advisory Commission (Cecchine et al., 2000; PAC, 1996, 1997) and PL 105–277 and PL 105–368. On the basis of those sources, this IOM committee reviewed the literature on the long-term adverse health effects of "insecticides," the classes of insecticides (such as organophosphorous compounds), and 12 specific insecticides and one insect repellent identified as having been used in the Persian Gulf. Although the committee also reviewed the literature on exposure to pesticides, it did not make conclusions of association on this broad category because it includes herbicides, fungicides, and other agents, known not to have been used during the Gulf War. Similarly,

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the committee reviewed the literature on the broad category of "solvents," the classes of solvents, and 53 specific solvents (Appendix D).

Although DOD sent rodenticides to the Persian Gulf, the committee did not review the health effects of rodenticide exposure. Inasmuch as those products were sent to the Persian Gulf in pellet form (Cecchine et al., 2000), exposure would have required ingestion. Because there were no accounts of military personnel consuming rodenticides, the committee did not believe it necessary to review their adverse health effects.

It should be noted, that the charge to IOM was not to determine whether a unique Gulf War syndrome exists or to make judgments regarding whether the veterans were exposed to the putative agents. Nor was the charge to focus on broader issues, such as the potential costs of compensation for veterans or policy regarding such compensation; such decisions are the responsibility of the secretary of veterans affairs. The committee's charge was to assess the scientific evidence regarding long-term health effects associated with exposure to specific agents that were potentially present during the Gulf War. The secretary may consider the committee's assessment as a compensation program for Gulf War veterans continues to be developed.

USE OF INSECTICIDES IN THE GULF WAR

Military personnel in the Gulf War were exposed to insecticides through field or personal use. Most used insecticides to control insects that could serve as vectors for infectious diseases, such as leishmaniasis, sand fly fever, and malaria. In addition to the list of insecticides congressionally mandated for study, the committee learned about insecticide use during the Gulf War from reports from DOD, the Office of the Special Assistant for Gulf War Illnesses (OSAGWI), surveys and self-reports from Gulf War veterans, and RAND (Cecchine et al., 2000; Fricker et al., 2000; OSAGWI, 2001; Spektor et al., 2000).

The specific insecticides and quantities shipped to the Persian Gulf can be documented, but how they were used and the amount each person was exposed to are unknown. Under contract with DOD, RAND conducted interviews with 2005 service members regarding specific insecticides and their use in the Persian Gulf. On the basis of reports of those interviews, the committee added azamethiphos, bendiocarb, and d-phenothrin to the list of insecticides congressionally mandated for study. The entire list of insecticides under review may be found in Appendix D.

According to DOD, most US service members had access primarily to two insecticides: permethrin and DEET. Permethrin was provided in spray cans for treating uniforms, and DEET in liquid or stick form was used as a personal mosquito and fly repellent. According to DOD, US service members were not provided with permethrin-pretreated uniforms. All other insecticides sent to the Gulf War were intended for use only by specifically trained people or for special applications (PAC, 1996). However, some service members reportedly used other, unapproved insecticides obtained on the local market, and pet tick and flea collars apparently were used by some US service members (OSAGWI, 2001).

All insecticides shipped to the Gulf War had been approved by the US Environmental Protection Agency (EPA) or the US Food and Drug Administration for

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general use in the United States (PAC, 1996) at that time. However, EPA has since placed restrictions on some of the insecticides used during the Gulf War.

USE OF SOLVENTS IN THE GULF WAR

To determine the specific solvents used in the Gulf War the committee gathered information from several sources, including veterans, OSAGWI (2000), and DOD's Defense Logistics Agency. As a result of its research, the committee ultimately identified 53 solvents for review (Appendix D).

There is little information to characterize the use of solvents in the Gulf War. Wartime uses of solvents (such as vehicle maintenance and repair, cleaning, and degreasing) probably paralleled stateside military or civilian uses of solvents, but operating conditions in the Gulf War (such as ventilation and the use of masks) may have varied widely from stateside working conditions.

The most thoroughly documented solvent exposure involved spray-painting with chemical-agent-resistant coating (CARC) (OSAGWI, 2000). Thousands of military vehicles deployed to the Gulf War were painted with tan CARC to provide camouflage protection for the desert environment and a surface that was easily decontaminated. Not all military personnel involved in CARC painting were trained in spray-painting operations, and some might not have had all the necessary personal protective equipment (OSAGWI, 2000).

Personnel engaged in CARC painting were exposed to solvents in the CARC formulations, paint thinners, and cleaning products. As noted in the OSAGWI report, some of the solvents used to clean painting equipment might have been purchased locally and therefore not identified.

COMPLEXITIES IN ADDRESSING GULF WAR HEALTH ISSUES

Investigations of the health effects of past wars often focused on narrowly defined hazards or health outcomes, such as infectious diseases (for example, typhoid and malaria) during the Civil War, specific chemical hazards (for example, mustard gas and Agent Orange) in World War I and Vietnam, and combat injuries. Discussion of the possible health effects of the Gulf War, however, involves many complex issues, such as exposure to multiple agents, lack of exposure information, nonspecific illnesses that lack defined diagnoses or treatment protocols, and the experience of war itself. The committee was not charged with addressing those issues, but it presents them here to acknowledge the difficulties faced by veterans and their families, researchers, policy-makers, and others in trying to understand Gulf War veterans' health.

Multiple Exposures and Chemical Interactions

Military personnel were potentially exposed to numerous agents during the Gulf War. The number of agents and the combination of agents to which the veterans may have been exposed make it difficult to determine whether any one agent or combination of agents is the cause of the veterans' illnesses. These include preventive measures (such as use of pyridostigmine bromide, vaccines, and insecticides), hazards of the natural environment

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(such as sand and endemic diseases), job-specific exposures (such as paints, solvents, and diesel fumes), war-related exposures (such as smoke from oil-well fires, depleted uranium, and stress), and hazards associated with cleanup operations (such as sarin and cyclosarin). Thus, Gulf War military personnel may have been exposed to a variety of agents concurrently. That most epidemiologic studies analyze single agents, not combinations of agents, makes it difficult to determine the effects of multiple wartime exposures and stressors.

Lack of Exposure Information

Determining whether Gulf War veterans face an increased risk of illness because of their exposures during the war would require extensive information about each exposure (for example, the agents, duration of exposure, route of exposure, internal dose, and adverse reactions). But very little is known about most Gulf War veterans' exposures and about their susceptibility to adverse effects.

After the ground war, an environmental-monitoring effort was initiated primarily because of concerns related to smoke from oil-well fires[4], and modeling efforts related to sarin exposure continue; however, there is sparse information on other agents to which the troops may have been exposed. Consequently, exposure data on most of the chemical agents are lacking or incomplete. Various exposure-assessment tools (such as global positioning systems) are being used to fill gaps in exposure information, but reconstruction of exposure events can never be completely accurate.

Unexplained Symptoms

Many Gulf War veterans suffer from an array of health problems and symptoms that are not disease-specific and are not easily classified with standard diagnostic coding systems. Population-based studies have found a higher prevalence of self-reported symptoms in Gulf War veterans than in nondeployed Gulf War-era veterans or other comparison groups (see Appendix A; Goss Gilroy Inc., 1998; Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999). Gulf War veterans do not all experience the same symptoms, and that has complicated efforts to determine whether there is a unique Gulf War syndrome. The symptoms suffered by many Gulf War veterans do not point to an obvious diagnosis, etiology, or standard treatment.

The War Experience

It has been documented from the Civil War to the Gulf War that the experience of war, with its many physical and psychologic stressors, places military personnel at high risk for adverse health effects. Some of the effects that have been reported are poorly understood multisymptom clusters, including fatigue, shortness of breath, headache, sleep disturbance, forgetfulness, and impaired concentration (Hyams et al., 1996). In World War II veterans, exposure to combat was associated with physical decline or death during the postwar period 1945–1960 (Elder et al., 1997). Similarly, combat exposure in Australian Vietnam veterans was related to reports of chronic mental disorders, ulcers, rashes, back disorders, and ill-

[4]Health effects of oil-well fires will be examined in *Gulf War and Health, Volume 3*, expected to be completed in the fall of 2004.

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defined conditions (O'Toole et al., 1996). Various labels have been used to describe such symptom clusters, including *shell shock, combat fatigue*, and *irritable heart;* but no single etiology has been determined (Hyams et al., 1996).

In addition to the threat or experience of combat, the Gulf War involved rapid and unexpected deployment, harsh living conditions, and continuous anticipation of exposure to chemical and biologic agents, environmental pollution from oil-well fires, and family disruption and financial strain. Each of those stressors—let alone all of them combined—may have had adverse effects on the health of many Gulf War veterans (IOM, 2001).

The committee, in responding to its charge, reviewed the literature on the agents associated with service in the Gulf War; it did not review the totality of the war experience (including pre- and post-deployment). The committee looked exclusively at the putative agents as though each one were the only risk factor for adverse health effects. The committee recognizes, however, that it might be important to look at the totality of the experience of war and its stressors, as well as at specific biologic, chemical, and radiologic exposures.

ORGANIZATION OF THE REPORT

Chapter 2 discusses the steps taken to identify and evaluate the literature and the criteria established by the committee to make conclusions of association. It also highlights many of the complex issues considered by the committee as the literature was reviewed. Chapters 3 and 4 are overviews of the toxicology of the relevant insecticides and solvents, respectively, and provide information on their short-term health effects in humans. Chapters 5–9 provide the committee's in-depth review of the epidemiologic studies of exposure to insecticides and solvents with regard to long-term adverse health effects. They present the committee's conclusions about the strength of the association between the putative agents and cancer (Chapters 5 and 6), neurologic effects (Chapter 7), reproductive effects (Chapter 8), and other health effects, such as dermatologic, renal, and hepatic outcomes (Chapter 9). There are several appendices in the report: Appendix A provides a discussion of the numerous studies of Gulf War veterans; the information offers background for the reader and provides a context for members of the IOM committee. Appendix B provides the conclusions and recommendations from Gulf War and Health, Volume 1. Appendix C provides a discussion of the methods used in searching the literature, while Appendix D includes a list of all insecticides and solvents identified as having been sent to the Persian Gulf. Appendix E provides a discussion and table of expected relative risks for lung cancer due solely to smoking for selected scenarios regarding the prevalence of smoking in the occupational cohort and in the general population. Appendix F describes the numerous neurologic tests that are used to diagnose neurologic health outcomes. Appendix G presents the committee's conclusions organized by health outcome rather than by category of association.

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2

IDENTIFYING AND EVALUATING THE LITERATURE

This chapter presents the methods used in identifying and evaluating the epidemiologic literature that form the basis of the committee's conclusions. It includes a description of basic epidemiologic study designs (such as cohort and case–control) and methodologic issues considered by the committee as it weighed the evidence for or against an association between exposure to insecticides or solvents and a health outcome. The chapter also includes a section on the nature and value of the experimental evidence of toxicity, which is discussed more fully in Chapters 3 and 4.

IDENTIFYING THE LITERATURE

As the committee began its task, the first step was to identify the literature that it would review. Searches were conducted by using the names and synonyms of the relevant insecticides and solvents identified for study (Chapter 1), their Chemical Abstracts Service registry numbers, and numerous occupations known to entail exposure to insecticides and solvents (such as pesticide applicators, painters, and dry cleaners). Background documents and reviews of experimental evidence were also retrieved and examined.

The literature search resulted in the retrieval of about 30,000 titles (Appendix C). As the titles and abstracts were reviewed, it became apparent that many of the studies were not relevant to the committee's task. The committee therefore developed inclusion criteria for the studies to be reviewed; for example, there had to be an examination of the agents under consideration, the design of a study had to be appropriate to the committee's task of weighing evidence, the study had to be an original study rather than a review or meta-analysis, and the results of the study had to demonstrate persistent rather than short-term effects. The criteria enabled the committee to narrow the 30,000 titles and abstracts to about 3000 peer-reviewed studies that it would review. The studies retained were primarily occupational studies of workers exposed chronically to insecticides and solvents, including studies of Gulf War veterans that specifically examined exposure to insecticides and solvents. Examples of those excluded from review were studies that focused solely on the efficacy of insecticide use in mitigating the effects of insect infestation or that examined pesticide ingestion and suicide. Similarly, studies of occupations with exposure to multiple agents (for example, farmers, agricultural workers) that did not address specific agents were excluded, as were studies of short-term outcomes.

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In addition to the above exclusions, it should be noted that animal studies had a limited role in the committee's assessment of association between the putative agent and health outcome. Animal data were used for making assessments of biologic plausibility in support of the human epidemiologic data rather than as part of the weight-of-evidence to determine the likelihood that an exposure to a specific agent might cause a long-term outcome.

The committee did not collect original data or perform any secondary data analysis. It did, however, calculate confidence intervals, when a study did not provide them, on the basis of the number of subjects, the relative risk or odds ratio, or the *p* value. Confidence intervals calculated by the committee are identified as such in the health-outcome chapters (Chapters 5–9).

DRAWING CONCLUSIONS ABOUT THE LITERATURE

The committee adopted a policy of using only published, peer-reviewed literature to draw its conclusions. Although the process of peer review by fellow professionals enhances the likelihood that a study has reached valid conclusions, it does not guarantee it. Accordingly, committee members read each study and considered its relevance and quality. The committee classified the evidence of an association between exposure to a specific agent and a specific health outcome into one of five categories. The categories closely resemble those used by several Institute of Medicine (IOM) committees that have evaluated vaccine safety (IOM, 1991, 1994a), herbicides used in Vietnam (IOM, 1994b, 1996, 1999), and indoor pollutants related to asthma (IOM, 2000). Although the first three categories imply a statistical association, the committee's conclusions are based on the strength and coherence of the findings in the available studies. The conclusions (Chapters 5–9) represent the committee's collective judgment.

The committee endeavored to express its judgment as clearly and precisely as the available data allowed, and it used the established categories of association from previous IOM studies because they have gained wide acceptance over more than a decade by Congress, government agencies, researchers, and veterans groups. However, inasmuch as each committee member relied on his or her training, expertise, and judgment, the committee's conclusions have both quantitative and qualitative aspects. In some cases, committee members were unable to agree on the strength of evidence of an association under review; in such instances, if a consensus conclusion could not be reached, the committee agreed to present both points of view in the text.

The five categories describe different levels of association and sound a recurring theme: the validity of an association is likely to vary with the extent to which the authors reduced common sources of error in making inferences—chance variation, bias, and confounding. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced.

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for

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sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, biologic plausibility, and a temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance[1] and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality[2] study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not[3] due to bias, including confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from well-conducted studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any

[1]Chance refers to sampling variability.

[2]Factors used to characterize high quality studies include, the statistical stability of the associations, whether dose–response or other trends were demonstrated, whether the association was among numerous comparisons that were made, and the quality of the assessments of exposure and outcome. Specifically, the quality of exposure assessment refers to specificity and sensitivity in relation to the association of interest. For instance, for insecticides, studies assessing specific insecticides (such as chlorpyrifos) have more specificity than those assessing classes of insecticides (such as organophosphorous), which in turn are more specific than those assessing pesticides more generally. With respect to sensitivity, studies are judged by the instruments used to measure exposure. Biologic monitoring data are theoretically the most preferable but are almost never obtainable in the context of a nonpersistent chemical and a disease with long latency, like cancer. Other kinds of efforts can obtain sensitive measures of exposure, such as use of occupational or environmental monitoring data, use of more extensive industrial hygiene assessments, use of interview techniques that help to minimize recall bias (for example, photos of products, and home and workplace walkthroughs). Similarly, there are questions about quality of outcome assessment–whether an outcome has been verified by a medical diagnosis in a consistent fashion.

[3]Factors used to make this judgment include the data on the relationship between potential confounders and related health end points in a given study, information on subject selection, and classification of exposure.

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magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

As the committee began its evaluation, neither the existence nor the absence of an association was presumed. Rather, the committee weighed the strengths and weaknesses of the available evidence to reach conclusions in a common format related to the above categories. It should be noted that although *causation* and *association* are often used interchangeably, the committee distinguishes between "sufficient evidence of a causal relationship" and "sufficient evidence of an association." An association can indicate an increase in risk without exposure to the putative agent being the sole or even primary cause.

Epidemiologic studies can establish statistical associations between exposure to specific agents and health effects, and associations are generally estimated by using relative risks or odds ratios. To conclude that an association exists, it is necessary for exposure to an agent to occur with the health outcome more frequently than expected by chance alone. Furthermore, it is almost always necessary to find that the effect occurs consistently in several studies. Epidemiologists seldom consider a single study sufficient to establish an association; rather, it is desirable to replicate the findings in other studies to draw conclusions about the association. Results from separate studies are sometimes conflicting. It is sometimes possible to attribute discordant study results to such characteristics as the soundness of study design, the quality of execution, and the influence of different forms of bias. Studies that result in a statistically precise measure of association suggest that the observed result was unlikely to be due to chance. When the measure of association does not show a statistically precise effect, it is important to consider the size of the sample and whether the study had the power to detect an actual effect.

Study designs differ in their ability to provide valid estimates of an association (Ellwood, 1998). Randomized controlled trials yield the most robust type of evidence, cohort or case–control studies are more susceptible to bias. Cross-sectional studies generally provide a lower level of evidence than cohort and case–control studies. Determining whether a given statistical association rises to the level of causation requires inference (Hill, 1965). To assess explanations other than causality, one must bring together evidence from different studies and apply well-established criteria (which have been refined over more than a century) (Evans, 1976; Hill, 1965; Susser, 1973, 1977, 1988, 1991; Wegman et al., 1997).

By examining numerous epidemiologic studies, the committee addressed the question, "Does the available evidence support a causal relationship or an association between exposure to a specific agent and a health outcome?" An association between a specific agent and a specific health outcome does not mean that exposure to the agent invariably results in the health outcome or that all cases of the health outcome result from exposure to the agent. Such complete correspondence between agent and disease is the exception in large populations (IOM, 1994b).

The committee evaluated the data and based its conclusions on the strength and coherence of the data in the selected studies. The conclusions expressed in Chapters 5–9 represent the committee's collective judgment. Occasionally, some committee members believed strongly that the literature supported, for example, a conclusion of "limited/suggested evidence of an association" while others concluded that the literature constituted "inadequate/insufficient evidence to determine whether an association exists." If

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a consensus conclusion could not be reached, both points of view are presented and discussed in the chapter, and the committee notes that further research is needed to resolve uncertainty. Each committee member presented and discussed conclusions with the entire committee.

EVALUATING THE LITERATURE

Epidemiology concerns itself with the study of the determinants, frequency, and distribution of disease in human populations. A focus on populations distinguishes epidemiology from other medical disciplines that focus on the individual. Epidemiologic studies examine the relationship between exposures to agents of interest in a studied population and the development of health outcomes, so they can be used to generate hypotheses for study or to test hypotheses posed by investigators. The following subsection describes the different types of epidemiologic studies and discusses the strengths and weaknesses of each.

Epidemiologic Study Designs

Ecologic Studies

In ecologic studies exposure to specific agents and disease are measured in populations as a whole. The data are presented as averages or rates within populations, and multiple populations are examined. For example, the exposure measurement may be the number of acres treated with insecticides or the per capita use of a particular agent. Morbidity or mortality from a specific disease is then mapped to the averages; each point represents a defined population with a specific biologic or chemical exposure and disease incidence. The correlation between the two variables among populations yields information for determining whether there is an association between exposure to the agent under consideration and outcome. Ecologic studies are not suitably designed to estimate risks for individuals. Indeed, associations found at the population level might not reflect associations at the individual level. Furthermore, the use of exposure measures based on per capita use tend to result in underestimation of any association, given that these variables are only proxies for what one would actually like to measure. But ecologic studies are useful for generating hypotheses and identifying agents that require further study. The most important limitation of ecologic studies is the lack of information at the individual level on other variables (confounding variables) that may explain an observed association between agent and disease.

Cross-Sectional Studies

A cross-sectional study provides a snapshot of a specific population at one point or over a short period in time. Exposure to the putative agent and disease are usually measured simultaneously. Information may be collected on numerous health conditions and current or past exposures to various agents. Disease or symptom prevalence between groups exposed or unexposed to a specific agent can be compared, or, conversely, exposure prevalence among groups with and without the disease can be examined. Although useful for generating hypotheses, cross-sectional studies are less appropriate for determining cause–effect

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relationships, because disease information and exposure information are collected simultaneously (Monson, 1990), and it may be difficult or impossible to determine the sequence of exposure to the putative agent and symptoms or disease. Such studies are most appropriate for examining the relation of biologic or chemical exposure to characteristics that do not change (such as blood group and race) or biologic or chemical exposure in situations for which current exposure is an adequate proxy of past exposure. A distinguishing feature of a cross-sectional study is that subjects are included without investigator knowledge of their exposure or disease status.

Cohort Studies

In a cohort study, a group of people who are free of the outcome of interest at a particular time are identified and followed for the occurrence of the outcome. At the beginning of followup, information is collected on exposure to a variety of agents; and the frequency of the outcome of interest during followup in those with and without a particular exposure of interest is compared. In each exposure group, the proportion of subjects who develop the outcome is computed (the risk) and the ratio of the risks (the relative risk, RR) in the two comparison groups is computed. Some cohorts (such as occupational groups) are identified on the basis of their exposure profile; in this case, a comparison group of presumably unexposed subjects can be compiled from other sources (such as national morbidity or mortality statistics). In this context, the measure of comparison is the standardized incidence ratio or the standardized mortality ratio, which takes into account differences in the age or sex distribution between the exposed cohort and the comparison group.

Cohort studies may be prospective or retrospective (historical), depending on whether the onset of disease or symptoms has occurred before (retrospective) or after (prospective) the initiation of the study. In a prospective cohort study, the exposure of interest may be present at the time of study initiation, but the outcome is not. In a retrospective cohort study, investigators begin their observation of the study subjects at a point in the past at which all subjects were free of the outcome of interest and recreate the followup to the present. The weakness of such study designs is their inability to measure multiple exposures. Retrospective cohort studies often focus on mortality rather than incidence because of the relative ease of determining the vital status of subjects in the past and the availability of death certificates to determine the cause of death.

The advantages of cohort studies are best demonstrated in circumstances involving rare exposure—because it can be targeted in the population identification (for example, in an occupational cohort)—or multiple outcomes. The strengths of cohort studies, particularly prospective cohort studies, include the ability to demonstrate a temporal sequence between the agent of interest and outcome and the minimization of selection bias at entry, inasmuch as all participants are presumed to be free of disease at baseline. A potential limitation of cohort studies, however, is the loss of study subjects during long periods of followup, which might result in selection bias if those lost to followup have a different exposure–outcome association from those who remain in the study.

Case–Control Studies

In contrast with how subjects are gathered for cohort studies, individuals are recruited into case–control studies on the basis of disease status. Subjects with the disease of

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interest are included as cases, and a comparison group, free of the outcome of interest, is selected as controls. A history of exposure to various agents among cases and controls is usually determined through standardized interviews of the participants or through proxies in the case of decedents or people unable to respond for themselves (such as those with cognitive impairment). Cases and controls may be matched with regard to such characteristics as age, sex, ethnicity, and socioeconomic status to balance the distribution of these variables in the two groups. The groups are then compared with respect to whether they have a history of exposure to the agent or characteristic of interest (Hennekens and Buring, 1987). The odds of exposure to the agent among the cases are compared with the odds of exposure to the agent among controls, and an odds ratio (OR) is computed. The case–control study is subject to a variety of forms of bias because disease has already occurred in one group. The biases and strategies to reduce them are discussed later in this chapter.

The case–control study is most useful for studying diseases with a low frequency in the population, in that it is often possible to recruit sufficient cases from a variety of sources. The challenge is the selection of a control group of people who would have been eligible for inclusion as cases if they had developed the disease (that is, those at risk for the outcome). Case–control studies are also useful for studying multiple exposure variables or determinants because the investigators can design data-collection methods (usually questionnaires) to obtain information on different aspects of exposure of the cases and controls. The cases may respond to questions about past biologic or chemical exposures differently from controls because the cases have already developed the disease. For example, they may overreport being exposed to specific agents in an attempt to "explain" their disease or might underreport such exposures. In either case, there is a potential for recall bias in which the tendency to report exposure to specific agents incorrectly is different for cases and controls. Finally, because a case–control study is conducted after a disease has occurred, special care has to be taken in assessing exposure to ensure that only exposures to the agent under consideration that occurred before onset of the disease are counted as being relevant to the question of etiology.

If living cases are not available, some case–control studies, called mortality odds ratio studies, use death certificates to determine both disease status and exposure. A person's "usual" or "last occupation" is often recorded on a death certificate and can be used to infer exposure. However, this information is often inaccurate or incomplete.

A more sophisticated variation on the classical case–control study is used increasingly—the nested case–control study. This form involves a sampling strategy whereby a case–control sampling takes place within an assembled cohort. In a nested case–control study, a cohort is identified and followed for the occurrence of the outcome of interest. Whenever a case of the outcome of interest is identified, a sample of the cohort who have not developed the outcome by that time are selected as controls. Information on exposure is then collected from both the cases and the selected controls. In some nested case–control studies, the cohort is assembled in such a way that information on exposure is collected on all subjects at baseline before disease occurrence (for example, blood samples are taken and stored). The advantage of the nested case–control design is that the most appropriate control group is chosen from members of the same cohort who have not developed the outcome at the time that they are chosen. In addition, exposures to the agent

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of interest need to be analyzed only for the cases and the selected controls rather than for the entire cohort, and this saves time and money.

Experimental Studies

Experimental studies in humans are the most reliable means of establishing causal associations between exposure to an agent of interest and human health outcomes. Key features of experimental studies are their prospective design, their use of a control group, and their random allocation of exposure to the agent under study. The randomized controlled trial is considered the most informative type of epidemiologic research design for the study of medications, surgical practices, biologic products, vaccines, and preventive interventions. The main drawbacks of randomized controlled trials are their expense, the time needed for completion, and the common practice of systematically excluding many groups of individuals, which limits the conclusions to a relatively small and homogeneous subgroup. Randomized trials are virtually non-existent as a means of determining the health risks of insecticides and solvents.

Measures of Association

The relationships that are examined in each type of epidemiologic study are quantified with statistical measures of association. In cohort studies, the measure of association between exposure to the agent of interest and outcome is the relative risk (RR), computed by dividing the risk or rate of developing the disease or condition over the followup period in the exposed group by the risk or rate in the unexposed group. An relative risk greater than 1 suggests that exposed subjects are more likely to develop the outcome than unexposed subjects, that is, it suggests a positive association between exposure to the putative agent and the disease. Conversely, a relative risk of less than 1 indicates that the agent might protect against the occurrence of the disease. A relative risk close to 1 indicates that there is little appreciable difference in risk (rates) and that there is little evidence of an association between the agent and the outcome.

In occupational cohort mortality studies, risk estimates are often standardized for comparison to general population mortality rates (by age, sex, race, time, and cause) because it can be difficult to identify a suitable control group of unexposed workers. The observed number of deaths among workers (from a specific cause, such as lung cancer) is compared with the expected number of deaths in an identified population, such as the general US population, accounting for age, sex, and calendar year. The ratio of observed to expected deaths produces a standardized mortality ratio (SMR). The SMR is usually a good estimator of relative risk; an SMR greater than 1 generally suggests an increased risk of dying in the exposed group. Less common, but identical in calculation, is a standardized incidence ratio (SIR). Incidence is a measure of new cases of a disease; mortality is the number of reported deaths. SIRs are calculated less often than SMRs, because disease incidence, as an end point, is often more difficult than death for investigators to identify and follow up. For disease mortality, death certificates are often used; they are easier to obtain than registry data that would indicate the incidence of a disease.

A proportionate mortality ratio (PMR) study relates the proportions of deaths from a specific cause in a specified time period between exposed and nonexposed subjects. That makes it possible to determine whether there is an excess or deficit of deaths from that cause

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in the exposed population. PMR studies can be misleading because their study design assumes that deaths from other causes are unrelated to the exposure of interest. The problem can be mitigated by selecting control causes of death on the basis of an assumed lack of association with exposure. The lack of direct measures at the individual level is an additional limitation of this study design. Unlike an SMR study that requires knowledge of the specific age, sex, race, or time within the exposed population at each stratum, a PMR study requires knowledge only of the proportion of cause-specific deaths in each stratum. Other complications involve the assignment of exposure to deceased subjects and a lack of temporal sequence.

In case–control studies, in contrast with cohort studies, it is not possible to estimate the risk of disease in each of the exposure groups because the number of subjects with the disease (the cases) is selected by the investigator. What can be computed, however, are the odds of exposure to the agent of interest in the cases and the odds of exposure to the agent in the controls. The ratio between those two quantities is an odds ratio (OR) that can be interpreted in much the same way as the relative risk. An odds ratio of 1 indicates no evidence of an association, odds ratio greater than 1 indicates the possibility of an increased risk, and an odds ratio less than 1 suggests a protective association. It can be shown mathematically that the odds ratio based on the odds of exposure to the putative agent in the cases and in the controls is identical with an odds ratio computed as the ratio of the odds of disease in the exposed group to the odds of exposure in the nondiseased group; this further justifies the use as an approximation to relative risk. The approximation is best when the prevalence of disease in the population is relatively low—precisely the situation in which a case–control study is used.

Ecologic studies use a different measure of association between exposure to the putative agent and disease. These studies map exposure averages to outcome rates by each population included. The measure of association, known as the correlation coefficient (r), estimates the degree to which the exposure to the agent of concern is related to outcome in a linear fashion. An r value can range from –1 to +1 and indicate both the strength and the direction of the association. A positive value close to 1 indicates a strong relation of outcome to exposure; a negative value close to –1 signifies a strong inverse relation. Values close to 0 indicate little or no relation between exposure and outcome. A key assumption is that the relation is linear. If the true relation between exposure and outcome is not linear but can be described by another curve (for example quadratic), the correlation coefficient will not be the most appropriate measure of the association. Graphic assessment of the relation is helpful in this regard.

Assessing the Validity of Findings

As described above, the goal of observational epidemiologic studies is to examine associations between exposures to particular agents and health outcomes in a population. However, the variability of individual experiences and the complexities involved in conducting studies in human populations, as opposed to the controlled laboratory setting, make it important to consider whether explanations other than causality might account for an observed association.

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Assessing the Effect of Chance

Statistical analysis provides a means to assess the degree to which an observed measure of association (such as RR, OR, SMR, SIR, and PMR) derived from a study reflects a true association. Using statistical analysis, one can assess the probability (sometimes called the *p* value) that an association as large or larger than the one actually observed could have been observed even if no true association exists, that is, could have arisen by chance. The magnitude of the *p* value is used as an aid to researchers in interpreting the results of a study. Typically, a *p* value of less than 0.05 is taken to be indicative that such a result would be "unlikely" if no true association existed and consequently provides evidence of a real association. A relative risk close to 1 indicates that there is little appreciable difference in risk (rates) and that there is little evidence of an association between the exposure and the outcome. In statistical terminology, a result is said to be "statistically significant" if the *p* value is smaller than 0.05. Lower (more stringent) *p* values may be used when multiple comparisons are being made. It is important to note that this preset value is arbitrary and is influenced not only by the size of the association but also by the size of the study sample. For example, if the sample is very large, even associations that are very small may be found to be "statistically significant." In contrast, a large association observed in a study with very few subjects might not be "statistically significant," primarily because of the sample size. Thus, in interpreting the results of statistical tests, it is critical to take into account not only the magnitude of the observed effect but also the size of the study sample. As a result, the committee decided not to rely on *p* values when evaluating the role of chance and did not identify studies as being "statistically significant." Instead, the committee focused on confidence intervals (CIs) as a more appropriate measure for assessing the association of interest.

A CI is the most likely range of values of the association in question and is based on the observed value of the association, its estimated variability if the study were to be repeated many times, and a specified "level of confidence." The confidence attached to the interval is actually in terms of the approach that is used rather than in the results themselves. Typically 95% CIs are presented. Thus, one interprets a 95% CI to mean that if the study were replicated 100 times (that is, if 100 samples were chosen from the same population, an association were measured, and a CI were constructed), 95 of the 100 CIs would contain the true value of the association. The width of the CI is influenced by the variability in the study data and by the sample size. Greater variability will increase the range, and increasing the sample size will result in a smaller range. CIs are the most appropriate way of presenting the results of epidemiologic studies because both the magnitude of the association and an assessment of the variability of the findings are provided.

Assessing the Effect of Bias

Various types of bias that are inherent in such studies may compromise the validity of epidemiologic study results. The biases may arise as a result of the choice of study subjects or of the way information on exposure or outcome is assessed. It is important that issues of bias be carefully examined in any review of evidence. In evaluating published studies, the committee considered the likelihood of bias and the possible magnitude and direction of effect of bias on the results.

Bias is a systematic error in the estimation of association between an exposure and an outcome that can result in deviation of the observed value from the true value. Bias can

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produce an underestimation or an overestimation of the magnitude of an association. Epidemiologic studies are subject to a variety of biases, and the primary challenge is to design a study as free of bias as possible. Bias may occur even if the utmost care is taken in designing a study. Researchers aware of the potential for bias can take steps to control it in the statistical analysis or interpretation of observed results. There are three main types of bias in epidemiologic research: selection bias, information (or misclassification) bias, and bias due to confounding.

Selection Bias

Selection bias can occur in the recruitment of study subjects to a cohort. For example, in a retrospective cohort study, when the exposed and unexposed groups are selected differentially on outcome, the assembled cohort can differ from the target population with respect to the association between exposure to the agent under study and disease outcome. In cohort studies of industrial populations, selection bias can operate at the time of entry or during followup. Furthermore, comparison of rates in the general population with rates in occupationally exposed cohorts may be subject to what is called the healthy-worker effect. This arises when a population that is healthy enough to be employed experiences lower mortality than the general population, which comprises healthy and unhealthy people. The healthy-worker effect can result in an underestimation of the strength of an association between exposure to an agent and some effect or outcome by failing to compare populations with similar levels of health. To balance the influence of the healthy-worker effect, some investigators divide worker populations into groups based on their levels of exposure to the agent being studied. Comparisons are then made within the cohort, thereby minimizing the healthy-worker effect.

Selection bias is of particular concern in case–control studies because the selection of study subjects is based on disease status. If exposed people were more likely to agree to participate than unexposed people, the study would produce an overestimation of the association in question—unless such selection is also present in the controls. In case–control studies, strategies to reduce the effect of selection bias generally concern the choice of control group.

Selection bias can also influence the results of a study through the pattern of missing data. If data are missing (because of a lack of response by subjects or because of errors in coding) in a way that is related to both the exposure of interest and the outcome, selection bias can occur.

Information Bias

Information bias (also known as misclassification bias) can occur when there are errors in data-collection methods, such as imprecise measurement of exposure or outcome. This is of concern, for example, when death certificates are used as a source of information on causes of death that are not verified. Inaccurate coding can create unknown error. The error may be uniform across the entire study population, in which case it may tend to reduce the apparent magnitude of associations (“bias toward the null”), or it may show up differently between study groups. Information bias in relation to the outcome can result from incorrect assignment of study subjects with respect to the outcome variable; a case may be misclassified as a control, or a member of a cohort during followup who develops disease will not be diagnosed, or vice versa. Such errors in classification of disease status are of

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particular concern if the error in classification is also related to the exposure status of the subject. For instance, if smokers are more likely to be diagnosed with emphysema than are nonsmokers with the same symptoms, the observed association between smoking and emphysema will be overestimated. However, misclassification of disease that is not related to exposure generally results in an underestimation of effect.

A number of factors may contribute to information bias in relation to exposure to the putative agent, including poorly designed questionnaires to determine actual exposures, differential recall of exposure between cases and controls, and differences in the interview process. Recall bias is of special concern in case–control studies: a differential likelihood of exposure reporting between study groups can be related to disease status rather than to the actual biologic or chemical exposure. The assumption is that cases would be more likely to report exposure to specific agents and to report it more fully. For example, a person with a chronic disease may be more likely than a healthy participant to report exposure to agents when queried in an attempt to determine the cause of the condition. Interviewer bias occurs, for example, when a questionnaire administrator is aware of a subject's disease status and inadvertently or intentionally solicits a particular response because of that knowledge.

Confounding

Confounding can occur when a variable related to the exposure and a risk factor for the outcome accounts for all or part of an observed exposure–outcome association. For example, if exposure to a given solvent appears to be associated with the development of lung cancer, cigarette smoking may confound this association if study subjects exposed to the solvent are more likely to have smoked than those not exposed. In this case, the observed relationship between exposure to solvents and lung cancer is said to be "confounded by" or "explained by" smoking. The effect of confounding can be minimized through study design (restriction or matching) or taken into account in the statistical analysis. In this example, restriction of the study subjects to nonsmokers would eliminate the possible confounding effect of smoking, although such a strategy may limit the generalizability of the findings. An alternative approach, most typically used in case–control studies, is to match each case to a control that has the same value of the confounding variable. For example, if age was suspected of confounding the relationship between exposure to insecticides and Parkinson's disease, investigators planning a case–control study might choose to match each case of Parkinson's disease to a control of the same age or within the same age range. Statistical techniques also are often used to reduce bias from known confounding factors.

Unmeasured Confounding in Cohort Studies. In cohort studies, it is common for mortality or incidence rates to be compared to rates in the general population and because of logistic difficulties there are often no measurements of confounding factors, such as smoking, available within the cohort. Comparisons of rates could be biased if there are large discrepancies in the prevalence of the risk factors in the cohort and in the general population. Methods have been developed (for example, Axelson, 1978) to estimate whether a confounding factor can explain the entire relative risk that has been observed in the cohort.

The general calculation is as follows: assume that there is no exposure effect in the cohort (i.e., exposure to solvents is not associated with the incidence of lung cancer). Let I represent the incidence rate in the cohort of the disease under study, let I_0 represent the

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incidence in the general population, let p_c represent the proportion of subjects in the cohort having the risk factor "c," and RR_c is the relative risk of the confounder.

Under the assumptions of no association with exposure and no synergy (the relative risks of the confounder are independent of exposure), the total incidence in the cohort is:

$$I = I_c \times p_c + I_0(1 - p_c) = RR_c \times I_0 \times p_c + I_0(1 - p_c) = I_0 \times \{1 + p_c \times (RR_c - 1)\} \quad (1)$$

The confounding relative risk (i.e., the relative risk due solely to the confounder that may be attributed mistakenly as being due to the exposure) is then the incidence in the cohort (I) divided by the incidence in the general population (I_g) (i.e., $RR=I/I_g$). A fundamental assumption is that only the confounder of interest increases the incidence rate above baseline (I_0).

This relationship can be generalized for risk factors that have many levels (e.g., moderate and heavy smokers), as follows:

Let I = incidence of a disease and $p_{c,i}$ the proportion of individuals having a risk factor c at level i. (2)

$$I = I_0 \times \sum_i \{1 + p_{c,i} \times (RR_{c,i} - 1)\}$$

For the purposes of illustration, let us take the example of lung cancer and smoking. In a cohort of workers exposed occupationally to solvents, assume that the observed standardized incidence rate (SIR) for lung cancer is two, but the prevalence of smoking in the cohort was not taken into account in the calculation. The question is: could this association be due to a higher rate of smoking among workers in the plant? No definitive answer can be given, however, equation (2) can be used with some realistic values of the proportion of workers smoking at varying intensities and the relative risk of developing lung cancer to obtain a series of expected relative risks under the assumption that there is no effect of exposure.

For example, assume that there is a cohort of subjects exposed to organic solvents and the end point is incidence from lung cancer. Assume further that:

- There is no association between lung cancer and exposure to organic solvents and only smoking increases the baseline incidence rate.
- The relative risks for smoking are assumed to be:
  - RR_c for moderate smokers = 10
  - RR_c for heavy smokers = 20

Table E.1 (Appendix E) shows detailed results under certain assumptions of the prevalence of smoking in the general population and in the occupational cohort. Some of the scenarios are rather implausible, for example, assuming that 70% of the population are heavy smokers. In cases where the prevalence of smoking in the general population exceeds that of the cohort, the expected relative risks are less than unity, meaning that an observed excess relative risk in the cohort would be underestimated because of confounding by smoking. Expected relative risks greater than unity, as would occur when there are more and heavier smokers in the occupational cohort, are interpreted as meaning that some of an observed effect could be explained by smoking. In the instance where all cohort members smoke heavily, the maximum relative risk that could be observed is 3.1. In general, the table shows

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that one requires extreme differential smoking patterns to explain observed relative risks above 1.5.

Exposure Assessment

Exposure assessment is important when considering the validity of findings because many epidemiologic studies use crude measurements in determining actual exposure experience. Working in a particular occupation, for example, is often used as a surrogate for exposure to a specific agent. Results of community-based air or water sampling also are often used as indicators of individual exposure to specific agents. For many biologic or chemical exposures, a personal history is a critical part of the assessment, but it is difficult to obtain retrospectively and can be obtained prospectively only with extraordinary effort (Rothman, 1993). The major difficulty that epidemiologists face is that there usually are at best limited records of area samples and only rarely any individual-specific exposure information. Consequently, the estimation of past exposure relies on indirect methods. The major result of this type of industrial hygiene investigation is that the estimates will be misclassified, which, if it is independent of outcome, will lead to attenuated estimates of relative risk. For current exposures, which are relevant for cross-sectional studies of prevalence of disease, making precise measurements is expensive but usually feasible.

Although we describe here the difficulty of assessing occupational exposures to organic solvents, the discussion pertains equally to many occupational exposures, including exposure to insecticides. Because exposure estimation is complex, we cover here only some of the major points that influence the interpretation of results of epidemiologic studies[4]. The discussion highlights many of the challenges that the committee members faced as they assessed a study's findings and drew conclusions about the strength of a reported association between a specific agent and a health outcome.

The methods used to assess occupational exposures to organic solvents depend on whether the interest is in current or past solvent exposure. In studies of cancer and other chronic diseases, it is usually assumed that exposures to substances in the distant past—for example, 10–20 years before the onset of disease—are the etiologically relevant ones. That is not always the case; for example, increasing time since last exposure to carbon disulfide appears to lower the risk of ischemic heart disease associated with it (Sweetnam et al., 1987). In cross-sectional studies, the interest is often in more recent or current exposures, although historical exposures might also be of interest in these studies.

Numerous methods are available for measuring current exposure, and these vary in complexity with the setting, the agent, and other factors. The selection of a method usually involves considerations of feasibility and of the balance between accuracy (validity and reliability) and cost. In increasing order of complexity and cost are methods that qualitatively provide estimates of magnitudes of exposure (for example, industrial hygienists familiar with the workplace use rank-ordered scales to attribute level of exposure on the basis of job title or other information related to tasks), methods that measure ambient concentrations in a plant or in specific areas, and methods that measure personal exposures (including biologic monitoring). The quantitative measurements can be coupled with other biologic values, such as breathing rates, and the use of toxicokinetics can be of value in

[4]For complete details, the reader is directed to more comprehensive reviews, such as *Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities* (NRC, 1991).

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estimating a dose to a target tissue, such as solvent concentration in the liver. In the case of solvents, one must remember that inhalation may be supplemented by other routes of exposure, such as dermal uptake and ingestion. Metabolites formed when the body attempts to detoxify itself might be more toxic than exposure to the solvent itself. There is usually considerable individual variability, so multiple measurements on a representative sample of workers, allowing for changes in frequency and intensity of exposure, need to be taken to arrive at accurate estimates. Biologic markers of exposure (for example, in blood, urine, or hair samples) can be useful for some solvents, but they might not accurately reflect exposure to solvents that are rapidly absorbed and excreted (Rosenberg et al., 1997).

Estimating historical exposures is very difficult. One must distinguish between different study designs; the main ones are retrospective cohort studies and population-based case–control studies. In cohort studies for which no exposure assessments have been conducted, the comparison is between rates of disease among workers in a plant, for example, and general population rates. Unless exposures are relatively homogeneous throughout the cohort, this method will provide inaccurate results. Investigating mortality patterns by department or job title can augment this study design, but again exposure measures can be highly misclassified if there is heterogeneity of exposure. Another type of cohort study is based on census records; one uses the census to identify individuals in different occupations at a given time and then follows them to determine mortality or morbidity rates. This study design can entail serious misclassification related to exposure heterogeneity and changes in jobs (and types of exposures) through the followup period. In a mortality odds-ratio study, a type of case–control study, death certificates are used to identify cases and controls, with the occupation recorded on the death certificate used as a surrogate of exposure. The occupation may be the last occupation or the "usual" occupation of a subject. Again, this can be highly inaccurate for the reasons cited above, and it can be especially misleading if workers change jobs as a result of illness.

For cohort studies in which investigators have access to the workplace facilities, a number of methods are available (Dosemeci et al., 1990; Stewart et al., 1986). When no actual measurements are available, the "gold standard" is as follows:

- An industrial-hygiene "walk-through" survey to enumerate current jobs and departments; to describe tasks, working conditions, processes, machines, and tools; and to catalog relevant chemical and physical agents.
- A detailed campaign of measurement of relevant biologic and chemical exposures.
- Characterization of historical tasks and chemicals used in departments and in jobs on the basis of estimates of material use, plant production records, hygiene controls and personal protective equipment, job and task description sheets, job and task safety analyses, process descriptions, engineering data on agents used and produced in the various industrial processes, and consultations with company engineers and other knowledgeable employees.

During the walk-through survey, additional information regarding exposure to each agent can be noted, including frequency of exposure, a subjective judgment of intensity of exposure, personal protective equipment used, and environmental controls used (such as exhaust fans). For departments no longer in operation, engineers and other knowledgeable company personnel can be interviewed and information similar to that obtained in the walk-through survey can be recorded.

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Because details of each subject's actual job tasks would generally not be known, although descriptions of departments and jobs by calendar year would usually be available from company records, the attribution of exposure would be based on an assessment of these data by experts—usually engineers, industrial hygienists, and chemists. A job-exposure matrix, which is essentially a set of rules that transforms a job to a set of indexes of exposure to specific agents, can be developed. The rows can represent jobs, and the columns exposures. Each cell of the matrix can contain an exposure index that is assigned in advance by the team; these indices can include estimates of the probability that exposure occurred, and average frequencies and intensities of exposure. Depending on the data, the latter can be coded on quantitative or qualitative scales. From this, one can assign to each worker various indexes of exposure to the agents under consideration. Standard cohort analyses (Breslow and Day, 1987) can then be used to estimate relative risk.

The above description represents the gold standard by which exposures to various agents are attributed in retrospective cohort studies. Prospective cohort studies can use the same approach but accuracy can be improved if a detailed measurement program is included. Such studies are rare and expensive.

In population-based case–control studies, a variety of methods have been used. The gold standard is now considered to be the method developed by Siemiatycki and his collaborators in Montreal (Gérin et al., 1985; Siemiatycki, 1991), as improved by Stewart and Stewart (1994a,b). When experienced chemical coders and interviewers are available, this procedure is thought to be superior to others (Bouyer and Hemon, 1993; Stewart and Stewart, 1994a,b), including the use of job titles and exposure information reported directly by subjects (Blair and Zahm, 1993; Bond et al., 1988; Joffe, 1992) and job-exposure matrices (Coggon et al., 1984; Dewar et al., 1991; Dosemeci et al., 1990; Hinds et al., 1985; Kromhout et al., 1992; Magnani et al., 1987; Olsen, 1988; Siemiatycki et al., 1989). Briefly, the method consists of using a structured interview to obtain details of every job that each subject held. The list is provided to a team of experienced chemists, industrial hygienists, and other experts who are familiar with the industries and jobs under consideration from their own personal experience and from in-depth reviews of the hygiene and industrial-process literature. The team then attributes exposure to a specified list of chemicals using rank-ordered scales for frequency, intensity, and reliability of their assessment. The scales can then be used in standard case–control analyses (Breslow and Day, 1980) to obtain estimates of relative risk by exposure, usually adjusted for other factors that are associated with risk.

Thus, numerous methods can be used to assess exposures in occupational settings. Epidemiologists must determine the reliability and accuracy of the methods as they interpret a study's results. Similarly, the committee members had to determine the validity of the methods as they weighed the evidence and drew conclusions about the literature.

Health Outcome Assessment

In addition to assessing the available information on the agent in question, the committee paid careful attention to the measurement of health outcomes. As is the case for exposure assessment, detailed and accurate information on the particular health outcome being examined leads to increased precision and increases the probability of detecting a true association between agent and a health outcome. In general, the disease or other health outcome should be defined as clearly as possible by using standard criteria and should be

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verified. Misclassification of a disease outcome can result in biased findings in an observational study, either in the inability to find an association that exists or in the reporting of a spurious association.

Information on a health outcome can be obtained in many ways in observational studies, including direct questioning of subjects about symptoms before diagnosis, clinical examination of subjects, medical-record review, and access to vital-statistics registries to determine diagnoses or causes of death of study subjects (Rothman and Greenland, 1998). There are a number of issues related to the use of each of those methods, including the reliability of self-reported symptoms, the accuracy of medical records, and variability in the degree to which death certificates correctly specify causes of death. Some studies include independent verification of diagnosis through pathologic confirmation. That reduces the probability of misclassification of outcome; but pathologic confirmation usually is not an option, and the use of death certificates continues to be the most common method of ascertaining cause of death. Diagnostic criteria and uniformity of disease coding have improved, and research has shown that cancer is coded accurately close to 82% of the time (Hoel et al., 1993). However, for cancers with low fatality rates, cancer-registry data should be used because of the potential for bias due to differential access to treatment. Improvements in reporting of death due to some specific cancers have led to apparent increases in the rates of cause-specific deaths that are probably artifacts of improved methods of diagnosis and reporting. But for other diseases—such as cardiovascular, respiratory, and neurologic disorders—death certificates generally are poorly coded.

Latency Period and Fatality Rate

Observational epidemiologic studies of diseases with long latency or high fatality rates, such as cancer, present a unique combination of challenges because of the difficulty of identifying all cases. The period between first exposure to the putative agent and disease onset is known as the latency period, during which cohort members may be lost to followup. In most instances, the latency period for cancer is believed to be long—5–20 years or longer—and probably depends not only on the type of disease but also on the concentration, duration, and intensity of the exposure and other factors, such as genetic predisposition. Few prospective studies are conducted on cancer outcomes, because of the long period of time before disease onset and the resulting costs. Instead, retrospective studies (either retrospective cohort studies or case–control studies) are conducted to examine the relationship between an agent that occurred in the past and the development of cancer.

Health outcomes, such as certain cancers, that have relatively high case-fatality rates reduce the number of living subjects available for inclusion in a study. Many studies therefore rely on mortality data rather than incidence data. However, the use of mortality data for health outcomes with lower fatality rates must be evaluated differently from those that still have relatively high mortality rates. The fact that exposed populations may have different access to medical care and consequently different survival rates may also bias the study results. In particular, there might be differences in early identification and treatment between exposed and nonexposed members of the population being studied.

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THE NATURE AND VALUE OF EXPERIMENTAL EVIDENCE

Scientific evidence regarding the potential for chemical substances to cause adverse health effects comes from studies in human populations (epidemiologic investigations) and from various types of laboratory (experimental) studies. The adverse health effects related to exposure to insecticides and solvents used during the Gulf War have been investigated both epidemiologically and experimentally in animals. Given its charge, the committee used primarily epidemiologic evidence to draw its conclusions of association. Toxicologic information provided additional information on plausibility and mechanism of toxicity, especially when making a conclusion of causality.

For most chemical substances, including the subjects of this report, far more data on the adverse health consequences of exposure can be found in the experimental literature than in the epidemiologic literature. The most telling and useful experimental data come from studies in experimental animals—typically rodents but also other species. In addition, much information is acquired from studies in isolated cells and other biologic systems (in vitro studies).

The use of experimental animals to study the adverse health effects of chemical substances began in the 1920s and evolved slowly until the 1960s, when the science of toxicology began to assume many of its modern attributes. In the last 30–40 years, experimental toxicology has provided a major source of information on the toxic hazards associated with exposures to industrial products and byproducts in air, water, food, soils, consumer products, and the workplace. This evolution in the role of experimental evidence came about, in part, because of increases in scientific understanding of how laboratory animals and other biologic systems could be used to provide reliable toxicity information.

In the early years of the discipline, studies tended to be relatively crude and were often limited to investigations of the consequences of a single large dose of a chemical (acute exposure), usually with the goal of defining lethal doses. Gradually, toxicologists added studies involving repeated daily doses; the earliest typically involved 90 days of exposure in rats and mice (a subchronic exposure, still a valuable source of data). In the late 1940s, some toxicologists developed and implemented chronic protocols, which were needed to detect slowly developing carcinogenic effects. Continued research provided the means to develop the specialized protocols used to study the effects of chemical exposure on the reproductive system and on the developing fetus. In more recent years, protocols related to the investigation of adverse neurologic and immunologic effects have been added to the list of reliable toxicologic methods. Much attention is now focused on studies of the behavior of chemicals in the body (toxicokinetic studies) and other types of investigations, designed to provide detailed understanding of the specific molecular and cellular events underlying the production of specific toxicity results. It is thought that mechanistic understanding will make the use of experimental data easier and more reliable for predicting health outcomes in humans.

Toxicologic studies have several important advantages over epidemiologic studies. Animal studies can provide data on toxic effects before the introduction of a chemical into commerce, and results from those studies can be used to establish limits on human exposure to avoid toxicity risks. Indeed, several federal laws require such premarket testing, with regulatory agency review to ensure the adequacy of the data and to establish safety limits. Epidemiologic studies can provide data only after human exposure has occurred. For

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diseases with long latency periods, such as cancer, meaningful results can be obtained only many years, or even decades, after human exposures began. In contrast, carcinogens can be identified in 2-year rodent studies.

It is possible to conduct well-controlled multidose experiments in animals so that quantitatively accurate dose-risk relationships can be obtained and causality firmly established. Two goals that are extremely difficult to achieve with epidemiologic studies. It is also possible to investigate a much wider range of adverse health effects in animals: at the end of the dosing period, for example, it is possible to undertake a complete pathologic examination of every organ and tissue of an animal's body. Such an examination cannot be undertaken in humans.

It is also possible to study the toxicity of any specific chemical in experimental animals. Epidemiologists are rarely able to identify human populations exposed to a single chemical of interest, so their work is often limited to groups of chemicals, sometimes poorly defined. That problem is prominent in the committee's reviews of epidemiologic studies of insecticides and solvents.

Animal studies, however, are also limited in several ways. It is generally not possible, for example, to evaluate subjective symptoms (such as headaches, joint aches, dizziness, and feelings of dejection) that are commonly reported by veterans of the Gulf War. (Even current clinical science is challenged when asked to study such phenomena; see Chapter 7.)

The most important limitation of animal studies is related to the simple and obvious fact that rodents, dogs, and even nonhuman primates are not human beings. It is well documented that some responses to toxic chemicals are similar among several species of animals, but it is equally well documented that others vary among species. The general similarity in biologic structures and functions in all mammalian species, including humans, tends to support the use of data from animal models to predict, with reasonably high certainty, adverse effects in humans. But prediction that an adverse effect observed in animals will also occur in sufficiently exposed humans is far more certain than prediction of the magnitude of the dose necessary to produce that effect in humans. That is, extrapolation of qualitative findings between species is more certain than extrapolation of quantitative findings.

A fairly large body of evidence supports the use of animal toxicity results to predict effects in humans. But there are still substantial uncertainties regarding the interpretation and predictive value of animal data. It is well documented that substances that have been identified through epidemiologic studies as human carcinogens (benzene, vinyl chloride, and many others) are also carcinogenic in rodents, but there is not always a good correspondence between the types of cancer observed in humans and those seen in rodents. It might be justified to conclude that animal carcinogens are highly likely to be human carcinogens, but it would be difficult to justify prediction of the type of human cancer expected. That is because animals lack the specificity needed for this study. While it might be adequate from the standpoint of a regulator to conclude that an agent can be classified as a carcinogen, this review requires linkage of that agent to a particular cancer site. But known human carcinogens may produce tumors in the same or in different sites in animals. For example, vinyl chloride, which is known to cause angiosarcoma of the liver in humans, causes zymbal gland tumors in male and female rats (along with a number of other cancer types including angiosarcoma). Humans do not have zymbal glands (NTP, 2002). Other uncertainties restrict

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our ability to draw inferences for human health from animal data. Where the available evidence supports the drawing of such inferences, however, failure to do so could lead to a mischaracterization of the human health effects of chemical exposures.

Notwithstanding the limitations in the predictive value of animal data, regulatory agencies, for the reasons described above, rely heavily on such data in assessing risks to humans and in establishing regulatory standards. There is, however, an element of a policy of caution in the regulatory uses of animal data, particularly when the scientific basis of extrapolation of specific types of animal results to humans is not well established. In the absence of adequate or convincing human evidence, regulatory officials act on the basis of animal findings to avoid neglecting a potential risk to humans. Most laws enforced by regulatory agencies permit the agencies wide latitude in the choice of data used to prevent future disease or injury. In the present case, however, the goal is not prevention of risk, but rather the use of the best available data to categorize evidence for a relationship between a chemical exposure and the occurrence of an adverse health outcome in humans. Here, precautionary policies have no substantial role (at least not the same way that they have in regulation). Therefore, studies in human populations played the dominant role for the committee in identifying the relevant associations. Experimental evidence may or may not provide support for epidemiologic conclusions.

Many of the chemicals that are discussed in this report have been subjected to extensive experimental toxicity studies, and all have been the subject of some level of study. A complete summary of all the experimental data available on all the solvents and pesticides or insecticides under review would fill volumes. Given the small role of such studies in this report in the categorization of evidence, such a detailed review would serve no purpose. Instead, the report provides only a broad picture of the most important experimental-toxicity data available in reliable secondary sources (Chapters 3 and 4). Relevant experimental data are discussed, however, in those chapters reaching conclusions of "sufficient evidence of a causal association" to support that categorization.

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3

INSECTICIDE TOXICOLOGY

Insecticides offer many benefits such as improved health of humans and animals, increased agricultural productivity, and reduced worldwide hunger. The use and misuse of insecticides, however, have been associated with health risks, environmental contamination, and poisoning (Ecobichon and Joy, 1994; Ecobichon, 2001; Ware, 1989). The toxicity of insecticides has been studied extensively in humans and animals (Ecobichon et al., 1990). Insecticides were used in the Gulf War to control insects that could serve as vectors for disease.

This chapter discusses the toxicity of several insecticides and classes of insecticides believed to have been used in the Gulf War including: organophosphorous compounds, carbamates, pyrethrins and pyrethroids, lindane, and *N,N*-diethyl-3-methylbenzamide (DEET). Although organophosphorous compounds and carbamates have similar mechanisms of toxicity and many insecticides have neurotoxic effects, it is difficult to summarize the general toxicity of insecticides. Therefore, the chemistry, toxicokinetics, genetic polymorphisms and susceptibilities, mechanism of action, human health effects of acute exposure, experimental data (including animal toxicity data and mutagenicity data), and available information on interactions with other agents are presented separately for each chemical class. Epidemiologic studies of the effects of chronic exposure to insecticides are discussed in the chapters on specific health effects (Chapters 5–9).

Although this chapter focuses on the active ingredients of insecticides, it is important to remember that the toxicity of an insecticide can be altered by its formulation. Agents contributing to formulation of an insecticide are often listed as "inert ingredients" (for example, petroleum products, xylenes, oils, and surfactants), but they can alter the toxicokinetics of an insecticide, potentially increase the absorption of active ingredients, and be toxic themselves (Petrelli et al., 1993; Ware, 1989).

ORGANOPHOSPHOROUS COMPOUNDS

Exposure to organophosphorous compounds can occur under a variety of conditions. Organophosphorous compounds are used as contact insecticides and are applied to crops, gardens, and domestic animals. Some organophosphorous compounds are used as systemic insecticides, in that they are taken up by the roots of plants and disseminated into stems and leaves. Others are used as ophthalmic agents, industrial chemicals (plasticizers and

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lubricants), and chemical-warfare agents. Organophosphorous compounds used as contact insecticides during the Gulf War include malathion, diazinon, chlorpyrifos, dichlorvos, and azamethiphos (Abou-Donia, 1995; Chambers and Levi, 1992; Ecobichon, 2001; Kamrin, 1997; Ware, 1989).

Chemistry

The structures of the organophosphorous compounds used as contact insecticides in the Gulf War are shown in Figure 3.1. Organophosphorous compounds that are used as insecticides contain a pentavalent phosphorus atom connected by esteratic, amide, or sulfur linkages to the organic portions of the molecule.

As esters or amides, organophosphorous compounds are chemically unstable and easily inactivated by hydrolysis. Organophosphorous compounds are lipophilic, some are oily liquids, and others are liquids that can be volatilized (Chambers and Levi, 1992; Ware, 1989).

Toxicokinetics

Toxicokinetics plays an important role in the toxicity of organophosphorous compounds. The oil-water partition coefficient, formulation, and route of exposure can affect the extent of and time needed for absorption. Dermal exposure can increase the time needed for absorption and ensuing toxicity. Almost 100% of the dermally administered dose of some of the highly lipophilic organophosphorous compounds can be absorbed. The potential for percutaneous absorption can be increased if formulations include petroleum products, oils, solvents, or surfactants or if occlusive dressings are placed on the skin (Ware, 1989).

Many organophosphorous compounds are supplied commercially in inactive forms (as protoxicants that need to be activated usually by liver mixed–function oxidases). For most organophosphorous compounds, that requires the change of the phosphorus–sulfur bond to a phosphorus–oxygen bond (for example, malathion needs to be oxidized to malaoxon, chlorpyrifos to chlorpyrifos-oxon, and diazinon to diazoxon). That bioactivation is catalyzed primarily by the P450 system. Dichlorvos and azamethiphos, however, are active without the need for biotransformation.

Detoxification of organophosphorous compounds involves hydrolysis, which can occur spontaneously in an aqueous environment. Hydrolysis can also be catalyzed by aryl and aliphatic hydrolases. Glutathione transferases and cytochrome P450s contribute to the detoxification of some organophosphorous compounds. Metabolic activation and inactivation of organophosphorous compounds occurs primarily in the liver, although other tissues also contribute. Extensive metabolism occurs via multiple pathways, and little, if any, unmetabolized organophosphorous compound is excreted.

Differences in biotransformation of organophosphorous compounds are important contributors to differences in potency and in susceptibility among species and individuals. In addition, the effects of organophosphorous compounds on biotransformation enzymes are important in interactions between the compounds and other chemicals (Ballantyne and Marrs, 1992; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991).

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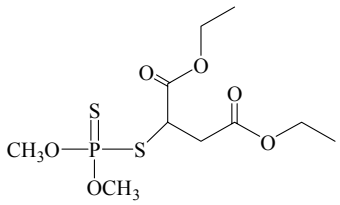
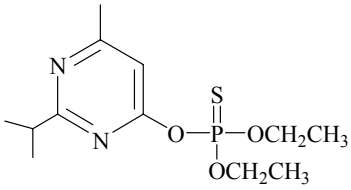
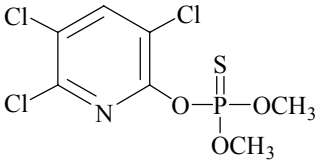


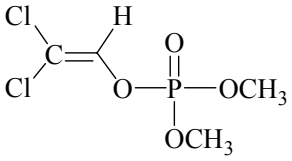
Malathion



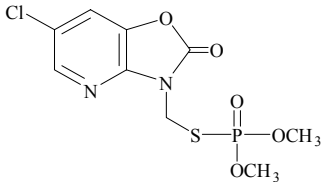
Diazinon



Chlorpyrifos



Dichlorvos



Azamethiphos

FIGURE 3.1 Structures of organophosphorous insecticides used in Gulf War.

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Genetic Polymorphisms and Susceptibility

Organisms can differ in the amounts and activities of their B esterases, and the differences affect susceptibility to organophosphorous compounds. Although acetylcholinesterase shows relatively little variation in structure and activity among individuals of a species, other esterases that interact with organophosphorous insecticides differ widely among individuals in a population. For example, several variants of pseudocholinesterase have been noted in human serum, with distinguishing differences related to capability for interaction with particular molecules (for example, succinylcholine and fluoride). A single clinical case report noted that atypical pseudocholinesterase was found in a soldier who suffered adverse effects when exposed to an acetylcholinesterase inhibitor during the Gulf War (Loewenstein-Lichtenstein et al., 1995). Differences in pseudocholinesterase activities did not, however, differentiate between symptomatic and asymptomatic Gulf War veterans when more subjects were studied (Kurt, 1998).

Differences in the biotransformation of organophosphorous compounds play a role in susceptibility to them in organisms of different ages and species. The young are generally more susceptible to acetylcholinesterase inhibition because they are less likely to convert organophosphorous compounds into nontoxic metabolites. Apart from age, different species have different capabilities for organophosphorous biotransformation; for example, avians can be 10 times as susceptible as mammals.

Genetic polymorphisms of A esterases (arylesterases) might play a role in susceptibility of humans and animals to organophosphorous compounds. Although other A esterases exist, the most studied are the paraoxonases, which metabolize, in addition to paraoxon, chlorpyrifos-oxon and diazoxon, the active metabolites of chlorpyrifos and diazinon, respectively, two organophosphorous insecticides used in the Gulf War. At least three gene products exist for paraoxonase. One of the gene products, paraoxonase-1 (PON1), has at least two isozymes (Q, formerly referred to as A; and R, formerly referred to as B). Those isozymes differ in their ability to metabolize organophosphorous insecticides. Population studies have demonstrated a trimodal distribution of paraoxonase activity, reflecting QQ, RR, and QR individuals. Reported individual differences in Q activities suggest that such differences contribute to the varied responses to environmental organophosphorous compounds in people and animals (Brophy et al., 2001; Cowan et al., 2001; Hernandez et al., 1999; La Du et al., 1999). In a small sample of Gulf War veterans, individuals with the neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the allele (Haley et al., 1999). Animal studies also demonstrate the role of PON1 in organophosphorous metabolism and the varying activity of the differential isozymes. PON1 knockout mice (mice without PON1) were found to be very sensitive to the toxicity of organophosphorous compounds, and following introduction of the enzyme to the knockout animals, the sensitivity to specific organophosphorous compounds varied with the isoform given to the animal. Animals given the Q isozyme were less sensitive to diazoxon while animals given the R isozyme were less sensitive to chlorpyrifos-oxon and paraoxon. It is important to note, however, that although mouse and human Q isoforms are similar, the catalytic efficiencies of their R isozymes differ (Furlong et al., 2000; Li et al., 2000).

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Mechanism of Action

Organophosphorous insecticides kill insects by affecting their nervous system. Specifically, they inhibit acetylcholinesterase, the enzyme that is responsible for the breakdown of acetylcholine and therefore the termination of its activity. Acetylcholine is a neurotransmitter that acts at two major receptor subtypes, nicotinic and muscarinic. Binding of acetylcholine to receptors at neuromuscular synapses leads to the activation of muscles. Failure to break down acetylcholine results in sustained activity and consequent overstimulation of cholinergically-mediated synapses, particularly nicotinic neuromuscular synapses, muscarinic parasympathetic synapses, and cholinergic synapses of the central nervous system (CNS). That mechanism of toxicity is the same in mammals, birds, and fish, so the acute effects are similar in humans and animals (Ecobichon, 2001).

Organophosphates inhibit acetylcholinesterase when the oxygen with the coordinate bond on the organophosphate molecule (see Figure 3.1) binds to the esteratic site of the acetylcholinesterase enzyme. That binding is initially reversible, but within a matter of minutes, part of the organophosphate molecule may be cleaved from the phosphorus group, and the remainder of the molecule will become essentially irreversibly attached at the esteratic site of the enzyme. The production of the essentially irreversible bond is called aging (Abou-Donia, 1995; Ballantyne and Marrs, 1992; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991; Marrs, 1996). Once aging has occurred, enzyme activity can be recovered only with the synthesis of new enzyme.

Acute Human Exposures

Immediate Effects

Clinical signs of toxicity associated with organophosphate-induced inhibition of acetylcholinesterase depend on dosage. Toxicity in humans and animals includes the signs associated with overstimulation of muscarinic receptors of the autonomic nervous system by acetylcholine (SLUD—salivation and sweating, lacrimation, urination, and defecation—as well as emesis and bradycardia). Acetylcholinesterase inhibition can also cause overstimulation (which can be followed by depression) of nicotinic receptors at neuromuscular junctions and autonomic ganglia and result in ataxia and fasciculations that, at higher dosages, can be followed by flaccid paralysis. Electromyographic changes can be observed after acute poisoning because nicotinic sites in muscles are affected; the changes include decreases in amplitude and increases in peak latencies in nerve conduction (Baker and Wilkinson, 1990; Gallo and Lawryk, 1991; Kaloianova and El Batawi, 1991). Stimulation of autonomic ganglia can also cause hypertension. As is the case at neuromuscular junctions, excess acetylcholine in the CNS causes stimulation that can be followed by depression. Overstimulation can be manifested as nervousness, delirium, hallucinations, and psychoses. Obvious signs do not generally appear until nervous system acetylcholinesterase inhibition approaches 70%.

Not all exposed people show all signs, and signs can vary with the organophosphorous compound, dose, route of exposure, and species. Signs often appear within minutes or hours, but they might not appear for several days. Duration can vary from minutes to weeks and can be followed by full recovery from obvious manifestations of

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cholinergic poisoning. If death occurs, it is due to respiratory failure, usually as a result of a combination of the autonomic effects mediated by the muscarinic and nicotinic acetylcholine receptors and the effects of acetylcholine at CNS receptors. Those effects include excessive fluid in the respiratory tract, paralysis of the respiratory muscles, and depression of the respiratory centers of the CNS.

Of the organophosphorous insecticides shipped from the United States to the Gulf War, oral lethal doses (LD_{50} values, doses that kill 50% of the animals tested) are highest for malathion (about 1 g/kg), intermediate for diazinon and chlorpyrifos (about 150–250 mg/kg), and lowest for dichlorvos (about 50 mg/kg) (Abou-Donia, 1995; Ballantyne and Marrs, 1992; Brown and Brix, 1998; Cecchine et al., 2000; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991; Kaloianova and El Batawi, 1991; Lotti, 2001; Marrs, 1996; Ware, 1989).

Diagnosis of organophosphorous-induced acute toxicity is based on exposure history, clinical manifestations of acetylcholinesterase inhibition, and laboratory findings. Erythrocyte acetylcholinesterase activity is used as an indicator of enzyme status in the nervous system. Metabolites of organophosphorous compounds to which humans and animals are exposed can also be detected in urine. Toxicity is unlikely to be overt unless blood acetylcholinesterase is substantially decreased (for example, by at least 50%; 70% inhibition is more likely to be correlated with clinical signs). Response to administration of atropine, an anticholinergic agent, has also been used as a diagnostic tool: poisoned organisms will not respond to atropine at doses that a nonpoisoned organism will respond to but require doses about 10 times higher before the expected pupil dilation, increased heart rate, and decreased secretions are noted (Ballantyne and Marrs, 1992; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991; Marrs, 1996).

Treatment for organophosphorous-caused acetylcholinesterase inhibition includes administration of atropine to antagonize acetylcholine stimulation of muscarinic receptors and administration of an oxime (such as pralidoxime) to regenerate acetylcholinesterase that is inhibited but not yet irreversibly bound. In the Gulf War and elsewhere, a carbamate compound (pyridostigmine bromide) has been used prophylactically when exposure to organophosphorous nerve gases was expected, because it inhibits but does not age the enzyme and so provides time for clearance of the organophosphate before sites on acetylcholinesterase are available to bind it irreversibly. Other treatments for acute acetylcholinesterase inhibition are not specific and consist of decreasing absorption, enhancing excretion, and addressing symptoms. Time is needed for recovery of acetylcholinesterase activity after aging because recovery requires synthesis of new enzyme. Weeks of supportive treatment might be needed if acetylcholinesterase remains sufficiently inhibited to cause signs of cholinergic poisoning (Ballantyne and Marrs, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Feldman, 1999; Gallo and Lawryk, 1991; Lotti, 2001).

Delayed Effects

Tolerance. Tolerance can occur after repeated exposure to cholinesterase-inhibiting organophosphorous insecticides. In general, tolerance can develop due to prolonged stimulation of cholinergic receptors by acetylcholine. Those receptors no longer respond as effectively to the neurotransmitter. Tolerance is more likely to occur at muscarinic than at nicotinic receptors and can develop when erythrocyte acetylcholinesterase is low but cholinergic poisoning is not overt (Bushnell et al., 1993).

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Tolerance can also occur when there is an increase in the proteins other than acetylcholinesterase to which organophosphorous compounds can bind. The alternative binding sites protect animals from organophosphate-induced acetylcholinesterase inhibition. Such sites include other esterases, notably pseudocholinesterase and carboxylesterases that are found in serum, liver, and other tissues. Although their precise physiologic role is unknown, those esterases can be involved in the metabolism of drugs and other compounds that contain ester and amide groups. Quantities of the alternative esterases, especially the carboxylesterases, depend on age, tissue, species, and exposure to agents that induce or inhibit enzymes. Agents that induce or inhibit enzymes include a number of drugs and other foreign compounds. When the esterases are induced, animals and humans are likely to be less susceptible to some of the organophosphorous compounds used as insecticides (Ballantyne and Marrs, 1992; Ecobichon, 2001; Gallo and Lawryk, 1991).

Intermediate syndrome. Clinical manifestations of acute acetylcholinesterase inhibition in humans or animals are not generally long-lasting or delayed, but there are exceptions. An "intermediate syndrome" has been described after severe poisoning: muscle weakness that occurs about 16 to 120 hours after exposure and 7 to 75 hours after the onset of acute poisoning symptoms (He et al., 1998; Shailesh et al., 1994). Overstimulation of nicotinic receptors followed by depression at neuromuscular junctions and muscle necrosis might be contributing factors. The muscle weakness can become severe and result in respiratory insufficiency. If respiration can be sustained, recovery occurs, although it can take weeks. Intermediate syndrome has been reported in humans after exposure to malathion and diazinon (Gallo and Lawryk, 1991).

Organophosphorous-induced delayed neuropathy. Another type of toxicity caused by a few organophosphorous compounds is a progressive, irreversible delayed neuropathy termed organophosphate-induced delayed neuropathy (OPIDN). OPIDN can occur in many species, including humans. Clinical manifestations of OPIDN include progressive, irreversible ataxia that develops weeks to months after exposure. Lesions are found in peripheral nerves and the spinal cord (Ehrich and Jortner, 2001).

OPIDN occurs only if organophosphorous compounds sufficiently, and essentially irreversibly, inhibit neuropathic target esterase (NTE) within hours of exposure. Inhibition of NTE is not related to inhibition of acetylcholinesterase, and organophosphorous compounds used as contact insecticides generally do not inhibit NTE. Organophosphorous compounds are tested for their potential to cause OPIDN before they are registered for use as insecticides, so most commercially available insecticides do not inhibit NTE. Commercially available insecticides that do inhibit NTE, such as chlorpyrifos and dichlorvos, do so only at doses that are sufficient to cause lethal cholinergic poisoning. OPIDN can occur only after rescue from acute chlorpyrifos or dichlorvos poisoning; even then it might not occur. At least six cases of OPIDN have been documented after ingestion of near-lethal doses of chlorpyrifos or dichlorvos (Aiuto et al., 1993; Lotti et al., 1986; Martinez-Chuecos et al., 1992; Vasilescu and Florescu, 1980); all but one occurred after unsuccessful suicide attempts. The absence of documented cases of OPIDN after exposure to diazinon or malathion is consistent with their lack of NTE inhibition in animal models. In fact, the chemical structures of malathion, diazinon, and azamethiphos make them exceedingly unlikely to inhibit NTE at all, and OPIDN has not been produced in experimental animals exposed to either malathion or diazinon (Ballantyne and Marrs, 1992; Cecchine et al., 2000; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy,

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1994; Ehrich and Jortner, 2001; Gallo and Lawryk, 1991; Johnson and Glynn, 2001; Kamrin, 1997; Lotti, 2001; Richardson, 1995).

Other delayed effects. Some studies have reported other persistent symptoms after poisoning with organophosphorous compounds or symptoms that appear 5–10 years after a poisoning episode, including neurologic and visual deficits, behavioral alterations, and impairment of cognition. Those effects, however, might be confounded by other factors or be the result of inappropriate study designs (Abou-Donia, 1995; Baker and Wilkinson, 1990; Chambers and Levi, 1992; Ecobichon and Joy, 1994; Eyer, 1995; Gallo and Lawryk, 1991; Jamal, 1997; Kaloianova and El Batawi, 1991; Lotti, 2001). Although some latent effects have been noted in laboratory rats, the symptoms reported in people have been difficult to verify in animal studies partly because of difficulties in replication of exposures and extrapolation of end points from humans to animals (Ballantyne and Marrs, 1992; Bushnell et al., 1993; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991; Marrs, 1996; Mattsson et al., 1996; Maurissen et al., 2000).

Experimental Data

Neurotoxic Effects

As noted above, organophosphorous insecticides increase levels of the neurotransmitter acetylcholine in both the central and peripheral nervous systems. Excess acetylcholine at neuromuscular junctions causes excessive neuromuscular stimulation (such as tremors), which can be followed by neuromuscular block. Excess acetylcholine at synapses of the autonomic nervous system affects quantity of secretions, heart rate, blood pressure, gastrointestinal function, urination, and pupil size. Excess acetylcholine at synapses of the CNS can alter behavior and cognition. Studies in animals generally require substantial inhibition of acetylcholinesterase (for example, greater than 40% inhibition of erythrocyte acetylcholinesterase) before those effects are seen. Even when doses of organophosphorous compounds are sufficient to cause notable evidence of cholinergic poisoning in animals or people, it is unusual for signs and symptoms to continue after recovery of acetylcholinesterase activity (Ballantyne and Marrs, 1992; Cecchine et al., 2000; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Eyer, 1995; Gallo and Lawryk, 1991; Marrs, 1996; Mattsson et al., 1996).

There has also been discussion around the potential effects of organophosphorous compounds on learning and memory following fetal and childhood exposures. In animals, however, some experiments have not demonstrated an increased sensitivity during the developing periods. Mattsson and colleagues (2000) treated rats with chlorpyrifos (0.3, 1.0, and 5.0 mg/kg/day) from gestational day 6 to postnatal day 10 and measured chlorpyrifos concentrations and cholinesterase inhibition in the fetuses and the dams. The nursing pups had a lower concentration than the dams and cholinesterase activity in all tissues of the high-dose pups rapidly returned to near control levels. Another study in rats with the same dosing regimen examined learning and memory, but no effects were seen in the absence of maternal toxicity (Maurissen et al., 2000).

Animal studies have been conducted to assess the persistence of neurotoxic effects of organophosphorous compounds. The results of a study of chlorpyrifos (at 1, 3, and 10 mg/kg per day, 5 days/week for 4 weeks followed by 4 weeks of recovery) do not indicate effects on short-term memory in adult rats, but do indicate a decrease in motor activity (Maurissen

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et al., 2000). Other reports noted locomotor reduction shortly after cessation of exposure and partial recovery of acetylcholinesterase inhibition in preweanling rats (Carr et al., 2001), long-term effects on cognitive end points in neonatally-exposed rats (Levin et al., 2001), and impairment of learning in preweanling rats and in rats immediately after weaning without regional brain acetylcholinesterase inhibition (Jett et al., 2001). Additional studies with relatively low, but cholinesterase-inhibiting, doses of other organophosphorous compounds have revealed behavioral and learning dysfunction in rats and in monkeys, especially after chronic administration (Eriksson and Talts, 2000; Prendergast et al., 1997, 1998).

In addition to their action as esterase inhibitors, some organophosphorous compounds have been reported to directly stimulate cholinergic receptors, including receptors of the heart and the nervous system, although concentrations might be higher than those needed for acetylcholinesterase inhibition (Chambers and Levi, 1992; Pope and Liu, 2001; Richardson, 1995).

Carcinogenicity

Organophosphorous insecticides, including those used in the Gulf War, are generally not considered carcinogenic. Long-term rodent studies of dichlorvos and malathion, however, have yielded mixed results (see ATSDR, 1997, 2001a; IARC, 1983, 1991; Kamrin, 1997; Van Maele-Fabry et al., 2000 for reviews).

Early studies in rats and mice did not show an increased incidence of tumors attributable to dichlorvos treatment (Blair et al., 1976; Horn et al., 1987, 1988). The National Toxicology Program (NTP) investigated the carcinogenicity of dichlorvos in feed in Osborne-Mendel rats (at 150 and 326 ppm) and B6C3F1 mice (at 318 and 635 ppm) (NTP, 1977); no evidence of increased tumor incidence attributable to dichlorvos was seen. More recently, NTP examined the carcinogenicity of dichlorvos given by gavage in F344/N rats (at 4 and 8 mg/kg per day, 5 days/week for 103 weeks in males and females) and B6C3F1 mice (males, at 10 and 20 mg/kg per day, 5 days/week for 103 weeks; females, at 20 and 40 mg/kg per day, 5 days/week for 103 weeks) (Chan et al., 1991; NTP, 1989). Some increased incidences of neoplastic effects were seen: in rats, adenomas of the exocrine pancreas (males and females), mononuclear cell leukemia (males), mammary gland fibroadenomas (females), combined fibroadenomas or adenomas (females), and multiple fibroadenomas (females); and in mice, squamous cell papillomas of the forestomach (males and females). In addition, two female mice developed forestomach squamous cell carcinomas. NTP concluded that there was "*some evidence of carcinogenic activity* of dichlorvos" in male F344/N rats and male B6C3F1 mice, "*equivocal evidence of carcinogenic activity* of dichlorvos" in female F344/N rats, and "*clear evidence of carcinogenic activity* of dichlorvos" in female B6C3F1 mice (Chan et al., 1991; NTP, 1989).

Evaluation of available data by the International Agency for Research on Cancer (IARC) resulted in the conclusion that there was inadequate evidence of the carcinogenicity of dichlorvos in humans but sufficient evidence in experimental animals. Therefore, dichlorvos was classified as a possible human carcinogen (Ballantyne and Marrs, 1992; IARC, 1991; Kamrin, 1997). A recent review of studies on the carcinogenicity of dichlorvos examining the length of the studies, confounding factors, and potential for bias has led the Health Council of Belgium to conclude that there is only sparse evidence that dichlorvos is carcinogenic in experimental animals and that it is not classifiable as to carcinogenicity in humans (Van Maele-Fabry et al., 2000).

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Animal studies of the carcinogenicity of malathion also have produced mixed results (see summaries in ATSDR, 2001a). In feeding studies conducted by the National Cancer Institute (NCI), no evidence of carcinogenicity was seen in Osborne-Mendel rats (at about 359 and 622 mg/kg per day for 80 weeks) (NCI, 1978), B6C3F1 mice (at about 1490 and 2980 mg/kg per day for 80 weeks) (NCI, 1978), and Fischer 344 rats (at about 166 and 322 mg/kg per day for 103 weeks) (NCI, 1979a). In a 2-year unpublished study in Fischer 344 rats with a wider dose range (2–868 mg/kg per day), however, some evidence of hepatocarcinogenicity (a statistical trend) was seen in female rats (Daly, 1996). Slauter (1994) treated B6C3F1 mice with 17.4–3448 mg/kg per day for 80 weeks. They saw an increase in the incidence of hepatocellular tumors with a positive dose trend, in both male and female mice at the two highest doses.

NCI also investigated the effects of malaoxon, the active metabolite of malathion, in Fischer 344 rats (at about 41 and 82 mg/kg per day for 103 weeks) and B6C3F1 mice (at about 91 and 182 mg/kg per day for 103 weeks) (NCI, 1979b). There was an increase in C-cell adenomas and carcinoma of the thyroid in female rats, but historical-control data led NCI to conclude that there was no evidence of carcinogenicity attributable to malaoxon (NCI, 1979b). NTP has since re-evaluated the histopathologic findings in the NCI studies (NCI 1978, 1979a,b) and concurred with most of the NCI conclusions, but concluded that for C-cell neoplasms of the thyroid gland after malaoxon treatment there is "equivocal evidence of carcinogenicity" in male and female Fischer 344 rats (Huff et al., 1985).

A 1983 IARC evaluation of malathion concluded that available data provided no evidence that malathion was carcinogenic in animals, and that it was unlikely to present a carcinogenic risk to humans (IARC, 1983). An EPA review of more recent information provided when malathion was evaluated for reregistration, however, resulted in the conclusion that there was "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential"; this was based on the appearance of liver tumors in rodents that were given doses of malathion considered excessive (US EPA, 2000).

Mutagenicity and Genotoxicity

Kamrin (1997) summarized results of mutagenicity tests of chlorpyrifos, diazinon, malathion, and dichlorvos. Mutagenicity tests of diazinon yielded inconclusive results, but malathion produced detectable mutagenesis in three types of cultured human cells. Dichlorvos binds to DNA and has been demonstrated to be mutagenic in vitro but not in vivo. Mutagenicity and genotoxicity tests yielded no evidence that chlorpyrifos has such activity (Gollapudi et al., 1995).

Reproductive and Developmental Effects

Organophosphorous insecticides have not historically been considered to be female reproductive or developmental toxicants at dosages lower than would cause acute maternal toxicity in mammals, although teratogenesis has been reported in fish and birds and endocrine changes in women (Baker and Wilkinson, 1990; Ballantyne and Marrs, 1992; Breslin et al., 1996; Kamrin, 1997).

Embryotoxicity, as indicated by decreases in body weight and skeletal size and a lag in development, has been reported in mice after administration of malathion at about 15–50% of the oral LD_{50} values, but no indication of maternal toxicity was provided (Asmatullah et al., 1993).

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Decreased pup weight and increased pup mortality were reported after administration of chlorpyrifos to rats. That occurred when pregnant female rats were exposed to chlorpyrifos at doses that caused maternal toxicity. Acetylcholinesterase inhibition was indicated by excessive salivation and tremors (Breslin et al., 1996). Decreased pup weight and increased pup mortality have also been reported in rats exposed to acetylcholinesterase-inhibiting doses of chlorpyrifos between birth and weaning (Carr et al., 2001). Biochemical changes other than acetylcholinesterase inhibition have been reported in neonatal rats exposed to chlorpyrifos, including changes in protein synthesis, DNA synthesis, intracellular signaling, and cholinergic receptors (Dam et al., 1998; Song et al., 1997; Tang et al., 1999; Whitney et al., 1995). Changes in righting reflex, cliff avoidance, locomotor activity, and spatial learning have been reported in neonatal, weanling, and juvenile rats exposed to chlorpyrifos at doses expected to inhibit acetylcholinesterase activity; some detriments occurred without notable enzyme inhibition or continued after substantial recovery of esterase activity (Carr et al., 2001; Chanda and Pope, 1996; Jett et al., 2001). The significance of behavioral changes in young rats with regard to possible toxicity in adult animals or in other species is unknown.

Immunotoxic Effects

The modulation of the immune system by malathion and its impurities depends on the dose, specific agent, cellular target, and duration of exposure; both stimulatory and suppressive effects have been reported in exposed animals. Dichlorvos has been reported to have suppressive effects on the generation of macrophages on chronic exposure and the ability to suppress cellular and humoral immune responses at cholinergic doses (Rodgers, 2001).

Other Health Effects

Dermatitis and hypersensitivities, including bronchospasm, have been reported after exposure to organophosphorous insecticides. The contributions of contaminants and vehicles to those responses have not been differentiated from effects of the active ingredients alone. Transient effects of malathion and dichlorvos on the immune system, including hypersensitivity and dermatitis, have been reported (Baker and Wilkinson, 1990; Chambers and Levi, 1992; Gallo and Lawryk, 1991; Kaloianova and El Batawi, 1991). Chlorpyrifos has been reported to increase lymphocyte numbers (Richardson, 1995).

Effects on respiratory, cardiac, and gastrointestinal systems in humans and animals are related to the ability of the insecticides to inhibit acetylcholinesterase and increase acetylcholine-mediated neural transmission (Ballantyne and Marrs, 1992). Some organophosphorous compounds—but not the insecticides used in the Gulf War—have been reported to have endocrine effects, including dysregulation of hypothalamic releasing factors when acetylcholinesterase was substantially inhibited (Smallridge et al., 1991), decreased spermatogenesis (Somkuti et al., 1991), increased estrogen metabolism (Berger and Sultatos, 1997), and antagonism at androgen receptors (Tamura et al., 2001).

Interactions with Other Agents

Organophosphorous insecticides can inhibit esterases other than acetylcholinesterase, including pseudocholinesterase and carboxylesterases in both humans and animals.

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Inhibition of those esterases can decrease the biotransformation of ester and amide drugs used in human and veterinary medicine—for example, local anesthetics, the neuromuscular blocker succinylcholine, such carbamates as neostigmine and pyridostigmine, and organophosphorous compounds used as ophthalmic agents and antiparasitic drugs. That inhibition would increase the duration of action of the drugs; sufficient inhibition of those esterases has the potential to result in drug toxicity (Ballantyne and Marrs, 1992; Chambers and Levi, 1992; Ecobichon, 2001; Ecobichon and Joy, 1994; Gallo and Lawryk, 1991; IOM, 2000).

Interactions are seen between organophosphorous insecticides and carbamates, another class of insecticides that also act by inhibiting acetylcholinesterases. The outcome of such interactions depends on dosage and sequence of exposure. Pretreatment with relatively low doses of carbamates will protect humans and animals from the irreversible acetylcholinesterase-inhibiting effects that can follow later exposure to organophosphorous compounds. That was the basis of the prophylactic use of the carbamate pyridostigmine bromide against organophosphorous nerve agents in the Gulf War (IOM, 2000). But simultaneous exposure to organophosphorous compounds and carbamates can result in exaggeration of acetylcholinesterase inhibition, which can also occur when exposure to carbamates follows exposure to organophosphorous compounds. Exposure to carbamates can also exaggerate the delayed neuropathy caused by some organophosphorous compounds (Ehrich and Jortner, 2001; Gallo and Lawryk, 1991).

It has long been known that the toxicity of cholinesterase inhibitors can increase with sequential exposure to cholinesterase inhibitors or other compounds detoxified by the same metabolic pathways. The enzymes that detoxify organophosphorous-insecticides are inhibited following the initial exposure, and would not be available for detoxification of a second organophosphorous insecticide (or other substrate) applied hours or days later because enzyme activity recovers slowly (Gallo and Lawryk, 1991). Interference with metabolism was thought to contribute to interactions seen in hens exposed to compounds used in the Gulf War, including chlorpyrifos. An increase in neurotoxicity (effects on locomotion and some neuropathologic changes) was seen when hens were treated with chlorpyrifos in combination with pyridostigmine, DEET, or both compared to hens treated with chlorpyrifos only (Abou-Donia et al., 1996). Biochemical alterations included a modest exaggeration in the decline of brain esterase activity when combinations of toxicants were used. The toxicity observed was not OPIDN but might have been the result of the combination of chemicals that have intrinsic neurotoxic potential. It should be noted, however, that the doses used were higher than those expected with human exposures and that hens are particularly sensitive to the neurotoxic effects of organophosphorous insecticides.

CARBAMATES

Chemistry

The use of carbamate insecticides began in the 1950s. About 50 carbamate compounds are in use today as insecticides or pharmaceuticals. Three carbamates were sent to the Gulf War: carbaryl, propoxur, and methomyl. Carbamates are *N*-substituted esters of carbamic acid. The structure of carbaryl, the prototype carbamate insecticide, is shown in

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Figure 3.2. The insecticidal carbamates were synthesized as analogues of physostigmine, the first carbamate, a toxic anticholinesterase alkaloid extracted from the calabar bean, the seed of the plant *Physostigma venenosum*.

Toxicokinetics

Carbamates are absorbed dermally and from the gastrointestinal tract. They are also readily absorbed after inhalation at temperatures at which vapors are formed. The rate and extent of absorption depend on the vehicle; oil vehicles virtually double oral toxicity (Goncharova, 1968). LD_{50} values are far lower with parenteral than with oral administration (Rybakova, 1966; Yakim, 1967). Once absorbed, the carbamates are distributed rapidly to tissues. The rate of elimination differs by route of exposure, but labeled compound or metabolite can be detected in blood, urine, and feces.

Biotransformation of carbaryl has been reported to be similar in humans, rats, guinea pigs, monkeys, and sheep, with the major difference being the extent to which carbaryl is hydrolyzed to yield 1-naphthol. It appears to be the primary metabolite (Baron, 1991). Other water-soluble metabolites, including unidentified conjugates that could be hydrolyzed by acid to thioethers, have been identified in the urine and bile of rats that received intravenous or intraperitoneal ring- or carbonyl-labeled carbaryl. In a study of rats, those metabolites accounted for up to 32% of the dose secreted in bile. Some evidence also suggests that carbaryl is oxidized to CO_2 in rats, guinea pigs, and humans. Small quantities of some intermediate metabolites of carbaryl are excreted in cows' milk.

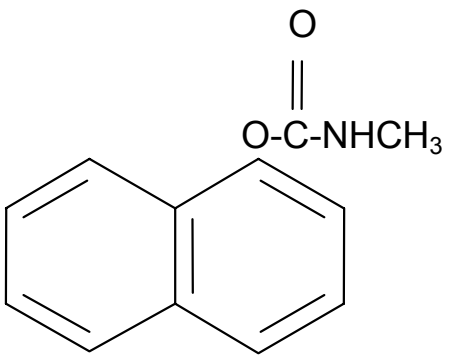

FIGURE 3.2 Structure of carbaryl.

Carbamate metabolism and excretion is relatively rapid. Mammals given naphthyl-labeled carbaryl, for example, excreted 68–74% of the label in urine and 2–11% in feces within 24 h of administration. Rats dosed with *N*-methyl[^{14}C]carbaryl eliminated 12–24% of the label in exhaled air and 53–54% in urine within 48 h. In another experiment, rats given carbonyl-labeled carbaryl eliminated 34–45% of the label in urine and 8% in feces within 24 h of administration; 30% was exhaled as $^{14}CO_2$ (see Baron, 1991 for review). Intratracheal instillation of radioactive carbaryl as an aerosol produced peak activity in blood within 2–5 min in rats; 90% of the radioactivity was recovered in urine and 2–5% in feces within 3 days. In a gavage study in mice, 69% of a dose of carbaryl was absorbed within 60 min, with a half-life ($t_{1/2}$) for absorption of 17 min. Peak blood concentrations occurred within 35–40 min after administration. By 60 min after administration, 16.9% of the dose appeared in urine and 8.6% in exhaled CO_2. In rats that received [^{14}C]carbaryl by gavage, the percentage of the administered dose recovered per gram of tissue ranged from less than 0.1% to 0.4% after 11 h; the highest concentrations were in liver, kidneys, and fat. Following an acute oral exposure of rats to carbaryl, it could be detected in the liver, brain, and heart 48 h after exposure.

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Genetic Polymorphisms and Susceptibility

Genetic polymorphisms and susceptibility have not been systematically explored with respect to carbamates. Two reports in humans might be pertinent. A pilot case–control study looked at the association between environmental exposure and acute leukemia in infants who were either positive or negative for a translocation involving chromosome band llq23[1] (that is, MLL^{+ve} and MLL^{-ve} infant acute leukemia). The data from that study indicate that fetal exposure to carbamate-based insecticides in some settings increased the odds ratio for infant acute leukemia but only in the presence of MLL^{+ve} rearrangements (Alexander et al., 2001). Those data suggest that MLL^{+ve} people might be more susceptible to carbamates. However, other mosquitocides might have been present, and the authors note limitations of the study, including the small number of cases and the potential nonrepresentativeness of controls. In addition, Loewenstein-Lichenstein and colleagues (1995) reported a soldier homozygous for "atypical" butyrylcholinesterase who experienced severe symptoms after pyridostigmine prophylaxis during the Gulf War.

In a rodent study, females exhibited greater sensitivity to carbaryl than males (Gaines, 1969).

Mechanism of Action

As with the organophosphorous insecticides, carbamate insecticides act by inhibiting acetylcholinesterase, the enzyme responsible for the breakdown and therefore the termination of the activity of acetylcholine. Failure to break down acetylcholine results in sustained effects of this neurotransmitter and consequent overstimulation of cholinergically mediated synapses, particularly nicotinic neuromuscular synapses, muscarinic parasympathetic synapses, and cholinergic synapses of the CNS (Ecobichon, 2001).

In contrast with the phosphorylation that occurs with organophosphorous insecticides, carbamylation of cholinesterase is reversible. Regeneration of the enzyme activity occurs within a few hours: the carbamate is cleaved and loses its ability to inhibit anticholinesterase.

Acute Human Exposures

As would be anticipated from its mechanism of action, the symptoms of carbamate-insecticide poisoning are similar to those of organophosphorous-insecticide poisoning. The clinical symptoms of acute exposure to carbaryl are derived from its effects on acetylcholine synapses, including actions at the synapses of the CNS and neuromuscular junctions, sensory nerve endings, ganglionic synapses of the parasympathetic and sympathetic nervous system, postganglionic sympathetic nerve terminals innervating sweat glands and blood vessels, sympathetic nerve terminals in the adrenal medulla, and postganglionic parasympathetic nerve terminals. Specifically, the effects stem from the accumulation of acetylcholine at those synapses. Carbamate toxicity typically involves the nervous and respiratory systems. Effects of peripheral muscarinic stimulation include increases in bronchial secretions and bronchoconstriction; excessive sweating, salivation, and lacrimation; pinpoint pupils; bradycardia; and vomiting and diarrhea. Effects of peripheral

[1]Translocations involving chromosome band llq23 occur frequently in hematologic malignancies.

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nicotinic stimulation include fine-muscle fasciculations and tachycardia. Various CNS manifestations also occur, including headache, respiratory depression, dizziness, anxiety, and mental confusion. Effects can progress to convulsions and coma (Ecobichon, 2001).

The combination of signs and symptoms that are exhibited depends on the specific chemical and the dose, duration, and route of exposure. Mild exposures typically produce only muscarinic and nicotinic signs, but severe exposures evoke CNS signs and pulmonary edema. Adverse effects can occur after dermal, inhalation, or ingestion exposure (Ecobichon, 2001).

The effects of carbamates are typically of shorter duration and milder than those of the organophosphorous compounds. Carbamates are not associated with OPIDN, but death has resulted from intentional administration of high doses of carbaryl (Ecobichon, 2001).

Experimental Data

Neurotoxic Effects

Because of its anticholinesterase activity, the transient effects of carbamates on the nervous system resemble those of cholinergic stimulation. In addition, acute exposures appear to change a variety of neurotransmitter systems in the CNS. Thresholds of such effects have not been determined.

Dietary exposure of swine to carbaryl resulted in a carbamate-induced syndrome that included neurotoxicity (Smalley, 1970; Smalley et al., 1969). Administration at 125–300 mg carbaryl/kg per day administered via the diet for 72–83 days resulted in myasthenia, incoordination, ataxia, tremor, muscle contractions, paraplegia, and prostration. At the higher dosages, those effects had a more rapid onset. The authors observed some recovery after exposure, but the effects recurred with micropathologic findings in the nervous system (Smalley, 1970; Smalley et al., 1969).

Carbamate exposure has behavioral consequences. Few systematic studies have addressed the behavioral effects, however, and they generally have been carried out with end points not considered especially sensitive. For example, acute exposure via various routes appears to decrease locomotor activity as measured in several devices. Decreases in wheel-running activity of rats were noted after acute exposure to carbaryl at only 0.56–2.24 mg/kg administered intraperitoneally. This was less than 4% of the LD_{50}, and the effect was reversed by atropine (Singh, 1973). Acute exposure results in persistent behavioral effects, including reductions in motor activity noted 72 h after oral doses of 20, 75, and 150 mg/kg (Moser, 1995**)**. Those doses represent 9, 33, and 65% of the reported LD_{50} for oral exposure of rats. Even at the lowest dose studied, autonomic function, motor activity, neuromuscular function, sensorimotor function, and reactivity are altered. An acute dose of only 10 mg/kg increased tolerance to electric shock and thereby attenuated the suppression of operant responding that also resulted in electric shock (Sideroff and Santolucito, 1972). Somewhat longer exposures to carbaryl may have the opposite effect on locomotor activity, reportedly increasing open-field activity and lowering the rate of habituation relative to controls.

An apparently unanswered question with respect to the carbamate insecticides is their effect on cognitive functions, including learning and memory. In a study of acute exposure to carbaryl in monkeys, dose-related decreases in accuracy (increases in errors) were observed in the repeated-learning paradigm after intramuscular injections of 1–10 mg/kg, whereas oral doses up to 50 mg/kg were without effects. Carbaryl was reported to be

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without effects on a working-memory paradigm in rats (Heise and Hudson, 1985a,b). In the only protracted-exposure study of carbaryl, Dési and colleagues (1974) reported a progressive increase in maze-running time and an increase in the number of associated errors in rats over the course of a 50-day exposure at 10–20 mg/kg in the diet. Additional studies with long-term, low-dose exposures and measures of effects on complex cognitive function are warranted and should include comparisons of effects after exposure by different routes.

Carcinogenicity

Several studies have examined the question of carbaryl carcinogenicity. In general, they have not provided any evidence of a relationship. The studies have been carried out in mice, rats, and dogs and have included exposures as long as 2 years (in the case of rats) (Gallo and Lawryk, 1991).

Mutagenicity and Genotoxicity

Substantial evidence has led to the assertion that methyl and dimethyl carbamates are not mutagenic as determined with a variety of assays for gene mutation, primary DNA damage, and chromosomal effects (WHO, 1986). Gene-mutation assays yielding negative results have included assessments of forward and reverse mutations in *Salmonella typhimurium*, *Escherichia coli*, *Bacillus subtilis*, yeast, in vitro rodent cells, host-mediated assays, and *Drosophila* sex-linked recessive lethal assays. DNA damage has been evaluated in bacteria, yeast, and human and rodent cells in vitro. Absence of chromosomal effects has been reported in *Drosophila*, in vitro rodent cells, in vivo rodent somatic cells, and dominant-lethal-mutation assays in rodents. Some reports of weak mutagenicity have been described at toxic doses, but the studies often had serious limitations that prevented interpretation of results. In in vivo cytogenetic studies in rats exposed to carbaryl, C-mitosis and additional mitotic abnormalities were noted. In 1980, the Environmental Protection Agency concluded that the totality of the available evidence did not support the assertion that carbaryl exposure is a risk factor for genotoxicity in somatic or germinal tissue of humans (Cranmer, 1986). A study of sister-chromatid exchanges (SCEs) and chromosomal aberrations in a pesticide-exposed population reported an increased frequency of SCEs in the symptomatic group, but the increase did not correlate with symptoms, and the group was exposed to a mixture of insecticides that included organophosphorous compounds, carbamates, and organochlorines (Dulout et al., 1985).

Reproductive and Developmental Effects

The reproductive and developmental toxicity of carbaryl has been examined in rats, gerbils, dogs, and primates following a variety of protocols, including multigeneration studies. Various effects have been seen. A 1-year oral exposure of rats at 3 mg/week was associated with decreases in spermatogonia and spermatozoa (Kitagawa et al., 1977). In several studies, decreases in viability, litter size, and survival have been noted. For example, in a three-generation reproductive study in rats, even the lowest dose (100 mg/kg per day) decreased weaning weights (Collins et al., 1971). In a three-generation study of gerbils, a dose of 150 mg/kg per day was found to be the no-observed-effect level; higher doses were associated with decreases in fertility, litter size, viability, and survival (Collins et al., 1971). In dogs, doses of 6–25 mg/kg per day (Smalley et al., 1968) and 2–12.5 mg/kg per day

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(Imming et al., 1969) resulted in teratogenesis. Notably, that teratogenesis was seen at doses similar to those at which fetotoxicity was not seen. Doses of 0.2–20 mg/kg per day on gestational days 20–38 resulted in no consistent evidence of fetotoxicity (Coulston et al., 1974).

More recently, effects on estrogenic and progesterone systems and the ability of carbamate insecticides to act as general endocrine modulators have been described. Klotz and colleagues (1997) reported, on the basis of in vitro studies, that the carbamates alone weakly activated estrogen- and progesterone-responsive reporter genes in breast and endometrial cancer cells. In whole-cell competition binding assays, the carbamates showed little capacity to displace radiolabeled estrogen or progesterone from its receptors. The effect of two carbamates, benomyl and carbendazim (at 500 and 1000 mg/kg for 5 days), on growth of decidua (the endometrium of the pregnant uterus) in pseudopregnant rats was assessed in an in vivo study. Both produced reductions in uterine decidual weight and uterine protein content, but serum estradiol and progesterone and the binding capacities of cytosolic estrogen and progesterone receptors were unchanged. The authors interpreted the findings as suggesting that antigrowth and antimitotic activities of the compounds on the decidua were direct and did not involve steroidal or receptor mechanisms.

Several reports have described effects on sperm due to carbaryl. When carbaryl at 50 and 100 mg/kg was fed to rats 5 days/week for 60 or 90 days, dose- and age-dependent declines in sperm count and motility and increased abnormal sperm structure were observed. The effects were more pronounced in young animals than in adults (Pant et al., 1995, 1996). Luca and Balan (1987) reported genotoxic effects in a sperm-abnormality assay in rats fed carbaryl for 3, 6, 9, 12, 15, and 18 months at 12.5, 25, and 250 mg/kg per day. Effects were generally dose-related, but they were not consistently observed for all exposure durations; maximal effects occurred at 6 and 15 months.

Other Health Effects

Chronic studies of carbaryl's effects on the immune system have revealed several effects. Doses of 2–8 mg/kg per day for 4 weeks resulted in immunosuppression in rabbits (Street and Sharma, 1975). A 9-month oral exposure of rats at 2 mg/kg per day resulted in changes in serum complement-fixing activity, lysozyme activity, and immune functions of the reticuloendothelial system, neutrophils, skin, and mucosa. That dose is less than 1% of the oral LD_{50} for rats. It is not clear from those reports to what extent the effects are accompanied by overt toxicity, loss of body weight, or other toxic outcomes. Furthermore, the studies did not determine the extent to which such effects are progressive or reversible.

Interactions with Other Agents

The aryl hydrocarbon receptor (AhR) is a transcription factor that activates gene expression, including expression of cytochrome P450 enzymes (such as CYP1A1), in a ligand-dependent manner. The environmental chemical dioxin is one of the most potent AhR ligands ever found. Data from an in vitro study indicate that carbaryl can induce CYP1A1 in human HepG2 and HaCaT cell lines (Ledirac et al., 1997), but that the effect occurs via AhR-independent mechanisms. More recent work (Denison et al., 1998), however, indicates that carbaryl indeed is a weak AhR ligand and inducer of AhR-dependent and dioxin-response-element-dependent gene expression in cell lines from other species. Whether that

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effect occurs in humans has yet to be evaluated, but the data suggest interactions between carbaryl and compounds that act via the AhR and between carbaryl and compounds that are metabolized by AhR-induced enzymes.

Carbaryl interacts with cimetidine (Tagamet®), a drug that blocks histamine-induced acid production in the stomach and is used to treat indigestion, acid reflux, heartburn, ulcers, and Zollinger-Ellison syndrome (Ward et al., 1988). May and colleagues (1992) investigated acetylcholinesterase activity in human red cells isolated 1 h after oral administration of carbaryl (at 1 mg/kg) to four healthy people who were taking or not taking cimetidine (at 300 mg every 8 h for 3 days). The results indicate additive effects of high concentrations of cimetidine and carbaryl on the inhibition of red-cell acetylcholinesterase, but no enhanced inhibition was seen at a therapeutically relevant concentration of cimetidine (10 µg/mL). Cotreatment with cimetidine doubled the peak plasma carbaryl concentrations and reduced clearance; carbaryl half-life was unchanged. Maximal inhibition of red-cell acetylcholinesterase activity was statistically significantly reduced. The concentration of carbaryl required to produce 20% inhibition was increased to about 0.5 µg/mL from 0.02 µg/mL. Those findings suggest that carbaryl is metabolized to bioactive metabolites by enzymes that cimetidine inhibits (May et al., 1992).

Mice pretreated with the liver microsomal-enzyme inducer phenobarbital were less susceptible to carbaryl toxicity; those treated with the inhibitor SKF525A demonstrated increased susceptibility (Neskovic et al., 1978). Other studies reported increased toxicity of carbaryl after pretreatment with reserpine or chlordiazepoxide and decreased toxicity after pretreatment with chlorpromazine or meprobamate (Weiss and Orzel, 1967). Tremor induced by carbaryl was substantially reduced by pretreatment with L-dopa and exacerbated by haloperidol; this suggests central catecholaminergic-dopaminergic mechanisms associated with tremor (Ray and Poddar, 1985). Pretreatment of rats with methylmercury hydroxide or chlordane accelerated the urinary excretion of carbaryl (Lucier et al., 1972).

Carpenter and colleagues (1961) reported that the effects of carbaryl were not altered by coadministration of other organophosphorous or other noncarbamate insecticides. However, Lechner and Abdel-Rahman (1986) reported that coadministration of malathion and carbaryl altered pharmacokinetic properties of both insecticides and delayed the elimination of ^{14}C-labeled carbaryl from the plasma of rats. Coadministration of acute equitoxic oral doses of other compounds—such as diphenyl, *o*-diphenyl, piperonyl butoxide, and thiabendazole—potentiated the effects of carbaryl in mice (Isshiki et al., 1983). Abu-Qare and Abou-Donia (2001) reported that combined exposures to the organophosphate chemical-warfare agent sarin (intramuscular) and the carbamate pyridostigmine bromide (oral) increased concentrations of 3-nitrotyrosine and 8-hydroxy-2-deoxyguanosine, biomarkers of oxidative stress. They also reported decreases in plasma butyrylcholinesterase activity and brain neurotoxic target esterase in hens after combined exposures to pyridostigmine (gavage), DEET (subcutaneous), and chlorpyrifos (subcutaneous) (Abou-Donia et al., 1996) and suggested the possibility that carbamates interact with other neurotoxic pesticides. In another study, however, dermal exposures to DEET did not influence absorption or dermal disposition of carbaryl (Baynes et al., 1997).

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PYRETHRINS AND PYRETHROIDS

Pyrethrins are insecticidal compounds that occur naturally in pyrethrum or chrysanthemum flowers (*Chrysanthemum cinerariifolium* and *C. coccineum*). Those flowers, which are grown mainly in Kenya, contain six toxins: pyrethrin I and II, jasmolin I and II, and cinerin I and II. Dried pyrethrum flowers and pyrethrum were used extensively as insecticides before World War II. They are potent insecticides with low mammalian toxicity, and they are relatively unstable under ultraviolet radiation and therefore degrade in the environment quickly (Matsumura, 1985; O'Brien, 1967). Use of pyrethrins declined after World War II with the advent of synthetic insecticides, such as DDT. In the 1960s, however, as concern about the harmful effects of some of those synthetic insecticides and their persistence in the environment grew, interest in the pyrethrins was renewed. A large number of pyrethrin derivatives, called pyrethroids, have since been synthesized and tested for insecticidal potency, mammalian toxicity, and biodegradability (Elliott, 1977). At least 2 dozen pyrethroids are in use today, and they make up one of the most popular classes of substances for control of agricultural and household insect pests. The rest of this section deals mainly with pyrethroids.

Two pyrethroids, permethrin and d-phenothrin, were used in the Gulf War. They were sprayed on military clothing to repel and kill flies and mosquitoes (Schreck and Kline, 1989; Schreck et al., 1986; Sholdt et al., 1989). Permethrin has also been used topically for treatment of head lice and scabies in humans (Asakawa et al., 1996; Facts and Comparisons, 2001; Fuortes, 1999; Llewellyn et al., 1996).

Chemistry

Pyrethrins and pyrethroids are esters of alcohols and acids (Elliott, 1977; Matsumura, 1985; O'Brien, 1967). Pyrethrins have excellent insecticidal properties, including a higher potency for insects than for mammals, but because they are relatively unstable in ultraviolet radiation, frequent application is necessary and can become expensive. Therefore, many pyrethroids with increased photostability have been synthesized (Elliott, 1977). Those pyrethroids may be divided into two large categories: type I pyrethroids, which do not contain a cyano moiety at the α position; and type II pyrethroids, which do contain an α-cyano group. Permethrin and phenothrin, the pyrethroid insecticides in this class used in the Gulf War, are type I pyrethroids. Other type I pyrethroids are resmethrin, allethrin, and cismethrin. Examples of type II pyrethroids are cypermethrin, fenvalerate, deltamethrin, and cyphenothrin (Ecobichon, 2001). The structures of pyrethrin I, permethrin, and *d*–phenothrin are shown in Figure 3.3.

Pyrethroids have two or three chiral carbon atoms, and the commercial pyrethroids are mixtures of four or eight isomers. Insecticidal activity varies greatly among isomers of a pyrethroid. For example, the most potent allethrin isomer against houseflies is d-allethronyl d-*trans*-chrysanthemate, and the least potent allethrin isomer is l-allethronyl l-*trans*-chrysanthemate; they differ in potency by a factor of 150.

Toxicokinetics

Pyrethroids are hydrophobic compounds that are absorbed and distributed after ingestion by mammals and inhalation exposure (ATSDR, 2001b). Dermal absorption is

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much slower than oral or inhalation exposure, and less than 2% of the applied dose is absorbed. Once absorbed, pyrethroids are distributed to most tissues, especially to those with a high lipid concentration. Pyrethroids are metabolized mainly via ester hydrolysis and oxidation at several loci of the structure. For example, permethrin is detoxified to at least 80 metabolites, including products hydroxylated at the *cis* and *trans* methyl groups (Casida et al., 1983). Metabolic enzymes include esterases and P450s. Most of the metabolites are inactive. Half-life varies among the different pyrethroid compounds, but range from 6.4 to 16.5 h in humans, with the elimination mostly complete within 5 d (ATSDR, 2001b). The metabolites are generally excreted as alcohols, phenols, carboxylic acids, and their glycine, sulfate, glucuronide and glucoside conjugates (ATSDR, 2001b).

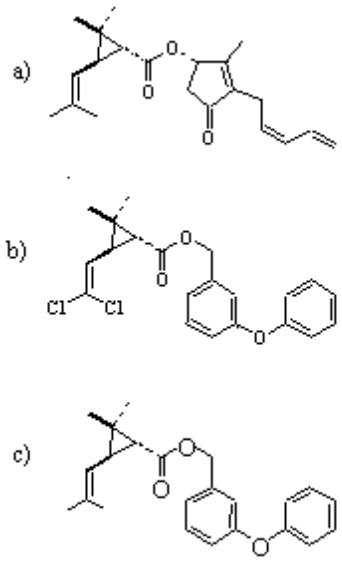

FIGURE 3.3 Structures of a) pyrethrin I, b) permethrin, and c) *d*–phenothrin.

Genetic Polymorphisms and Susceptibility

No information specific to pyrethroids is available on genetic polymorphisms. Young rats have been shown to be more sensitive than adults to an acute lethal dose of type II pyrethroids, but no differences in age-related sensitivity were seen in response to lower doses. No age differences in sensitivity to type I pyrethroids were seen (Sheets, 2000). Other investigators, however, have demonstrated that fetal or young rats and mice are sensitive to the neurochemical and neurobehavioral effects of pyrethroids (Aziz et al., 2001; Eriksson and Fredriksson, 1991; Husain et al., 1994; Lazarini et al., 2001).

Mechanism of Action

Type I and type II pyrethroids exert their toxicity by affecting the voltage-gated sodium channels of neurons (Narahashi, 1996, 2001; Soderlund et al., 2002; Vijverberg and van den Bercken, 1990). Slowing of the kinetics of activation and inactivation of the gates of the sodium channel by the pyrethroids results in a prolonged opening of individual sodium channels from the normal few milliseconds to several hundred milliseconds by type I pyrethroids and as long as several seconds by type II pyrethroids.

Type I and type II pyrethroids produce the T syndrome and the CS syndrome, respectively (see "Experimental Data" for descriptions of symptoms). In both syndromes, sodium currents of whole cells are greatly prolonged, and this leads to an increase in the depolarizing after-potential or a membrane depolarization. In the T syndrome, type I pyrethroids increase and prolong the depolarizing after-potential and generate repetitive after-discharges. In the CS syndrome, type II pyrethroids generally cause membrane depolarization that evokes repetitive discharges. There is also evidence that type II pyrethroids block the chloride-ion channel of the γ-aminobutyric acid-receptor channel complex (Ecobichon, 2001). To increase the depolarizing after-potential to the threshold for inducing repetitive discharges, only about 1% of the sodium-channel population of rat brain

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neurons needs to be modified (Song and Narahashi, 1996); that is why pyrethroids are so potent.

Acute exposure to the type II pyrethroid deltamethrin induces apoptosis in the rat brain that might be associated with the neurodegeneration seen after exposure (Wu and Liu, 2000). Persistent increases in p53 and Bax expression and transient increases in Bcl-2 expression that were seen immunohistochemically after deltamethrin treatment of rats could contribute to the apoptotic cell death (Wu et al., 2000).

Pyrethroids are much more potent in insects than in mammals; the difference in LD_{50}s is a factor of about 4500 (Elliott, 1976). The major factors underlying the selective toxicity of pyrethroids in insects are sodium-channel sensitivity and temperature dependence (Song and Narahashi, 1996). Insect sodium channels are 100–1000 times more sensitive to pyrethroids than are mammalian sodium channels (Narahashi, 2001; Warmke et al., 1997). Furthermore, the activity of pyrethroids is temperature-dependent; they have a greater effect on sodium channels at lower temperatures than at higher temperatures. For example, potency increases by a factor of 5 if temperature is lowered by 10°C (Song and Narahashi, 1996). Because insects have a lower body temperature (about 27°C) than mammals (about 37°C), temperature dependence contributes to the selective toxicity in insects. A difference (by a factor of about 3) in the rate of pyrethroid detoxification between mammals and insects also contributes to the selective toxicity.

Acute Human Exposures

Ray and Forshaw (2000) review pyrethroid poisonings. Accidental spilling of pyrethroids on the head, face, and eyes caused pain, lacrimation, photophobia, congestion, and edema of the conjunctiva and eyelids (He et al., 1988, 1989). Acute ingestion of pyrethroids was reported to cause epigastric pain, nausea, vomiting, headache, dizziness, anorexia, fatigue, tightness in the chest, blurred vision, paresthesia, palpitations, coarse muscular fasciculations, and disturbances of consciousness (He et al., 1988, 1989).

Cutaneous paresthesia is a general effect seen after exposure to all pyrethroids and pyrethrins. It is reversible and not accompanied by electrophysiologic, clinical, and persistent abnormalities. Type II pyrethroids tend to be more potent toxicants than type I pyrethroids (Aldridge, 1990; Flannigan and Tucker, 1985; He et al., 1988, 1989; Knox et al., 1984; Kolmodin-Hedman et al., 1982; LeQuesne et al., 1981; Litchfield, 1985; Tucker and Flannigan, 1983; Vijverberg and van den Bercken, 1990). There have been reports of contact dermatitis (Bainova, 1987; Tomova, 1982), but the dermal toxicity is not considered serious (Bradbury and Coats, 1989; Miyamoto, 1976).

Acute inhalation of type II pyrethroids has been reported to have irritating effects on the mucous membranes of respiratory passages (Vijverberg and van den Bercken, 1990). Asthma-like attacks and anaphylactic reactions with peripheral vascular collapse were reported after exposure to pyrethrins (ATSDR, 2001b).

Altenkirch and colleagues (1996) reported on the neurological examinations of 23 reported cases (out of 64) of pyrethroid poisoning. Exposures were to permethrin, deltamethrin, cyphenothrin, tetramethrin, and mixtures of various pesticides. In nine cases, severe somatic or psychiatric disorders were present that had no plausible relationship to the chemical exposure. Cullen (1987) reported that eight people developed multiple chemical sensitivity syndrome after exposure to pyrethroids. In six cases, a causal link between acute

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symptoms and pyrethroid exposure seemed likely or could not be ruled out. No evidence of irreversible peripheral or central nervous system lesions was found in any case.

Experimental Data

Neurotoxic Effects

Type I and type II pyrethroids cause different acute symptoms in rats, the animal species in which most toxicity studies of pyrethroids have been conducted (Aldridge, 1990; Vijverberg and van den Bercken, 1990). Type I pyrethroids, such as those used in the Gulf War, do not have the α-cyano moiety and cause what is called the T syndrome. The T syndrome is characterized in rats by aggressive sparring, hypersensitivity to external stimuli, whole-body tremor, and prostration. Type II pyrethroids, which contain an α-cyano group, cause the CS syndrome. The CS syndrome is characterized by burrowing behavior, profuse salivation without lacrimation, coarse tremors, clonic seizures, and sinuous writhing (choreoathetosis). Type II pyrethroids are also known to increase cardiac contractility (Forshaw and Bradbury, 1983). Some pyrethroids, such as fenproponate, cause mixed or intermediate T and CS motor syndromes (Lawrence and Casida, 1982; Wright et al., 1988). Some other pyrethroids, such as fenproparthrin, produce an intermediate TS syndrome characterized by tremors and salivation.

Acute near-lethal and lethal doses of type II pyrethroids cause axonal swelling and demyelination in the sciatic nerve of the rat (FAO/WHO, 1980; Parker et al., 1985). Near-lethal doses of both type I and II pyrethroids have also been reported to cause sparse axonopathy of rat sciatic and posterior nerves (Aldridge, 1980, 1990; Vijverberg and van den Bercken, 1990).

Chronic neurotoxicity has been reported after pyrethroid exposure in some animal experiments, but the toxicity was usually either low or absent. Little or no chronic neurobehavioral or neurohistologic toxicity has been reported after administration of pyrethrins and pyrethroids, including permethrin (Aldridge, 1990; Bainova et al., 1986; Extoxnet, 1994; Thomson, 1985; Vijverberg and van den Bercken, 1990). Axonal swelling and myelin degeneration have been reported only after repeated or high doses of permethrin, cypermethrin, or fenvalerate (Extoxnet, 1994; FAO/WHO, 1980; Rose and Dewar, 1983). Increased brain concentrations of β-glucuronidase, β-galactosidase, and alkaline phosphatase have also been seen (Dewar, 1981; Dewar and Moffett, 1979).

Carcinogenicity

Chronic application of most pyrethroids tested, including permethrin, rarely and inconsistently caused cancer (DuPont de Nemours Corp., 1989; Extoxnet, 1994; Hallenbeck and Cunningham-Burns, 1985; Ray, 1991; US EPA, 1988, 1989; Waters et al., 1982). One exception is cypermethrin, which was reported to cause benign lung tumors in female mice (US EPA, 1989). Shukla and colleagues (2001) demonstrated that deltamethrin has tumor initiating, but not tumor promoting, activity for skin tumorigenesis in mice.

Mutagenicity and Genotoxicity

One type II pyrethroid, cypermethrin, was tested and found to have no mutagenic or genotoxic effects (FAO/WHO, 1980; Pluijmen et al., 1984; Waters et al., 1982). It was reported, however, to increase polychromatic red cells with micronuclei in bone marrow in

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mice (Amer and Aboul-ela, 1985); the clinical significance of this finding is unknown. No mutagenic activity was detected in three in vitro assays for decamethrin (Kavlock et al., 1979). Pluijmen and colleagues (1984) found a lack of mutagenic activity of cypermethrin, permethrin, deltamethrin, bioresmethrin, resmethrin, cismethrin and fenvalerate in *S. typhimurium* strains. Herrera and Laborda (1988) found no mutagenic activity in *S. typhimurium* with resmethrin, permethrin and fenvalerate, but did not find mutagenic activity with allethrin in some *S. typhimurium* strains with or without metabolic activation.

Reproductive and Developmental Effects

In an in vitro test system, none of the eight pyrethroids tested showed substantial estrogenic or antiestrogenic effects at 100–10,000 nM. In vitro tests also showed that they did not alter human estrogen-receptor α-mediated mechanisms (Saito et al., 2000; Sumida et al., 2001).

In general, chronic administration of pyrethroids to female rats does not effect the development of their offspring (Extoxnet, 1994). Pyrethroids are not gonadotoxic, embryotoxic, or teratogenic (Hallenbeck and Cunningham-Burns, 1985; Kaloianova and El Batawi, 1991; Kidd and James, 1991; Litchfield, 1985; Miyamoto, 1976; Polakova and Vargova, 1983; Ray, 1991; US EPA, 1983). High oral doses (250 mg/kg per day) of permethrin during gestational days 6–15, however, reduced the number of offspring (Wauchope et al., 1992). A three-generation study of resmethrin reported slight increases in premature stillbirths and a decrease in pup weight (Ray, 1991). Taken together, the data suggest that pyrethroids are unlikely to cause reproductive and teratogenic effects (Kamrin, 1997).

Immunotoxic Effects

Although detailed studies of the effects of pyrethrins and pyrethroids on immune measures have not been conducted, permethrin has been reported to suppress immune responses in animals. The toxicological significance of these effects to human exposures, however, is difficult to determine because few studies have been conducted in humans and because of interindividual variability (ATSDR, 2001b). Exposure of chickens to a low dose of permethrin in the diet (0.1 ppm) for 3–6 weeks after hatching reduced their immune responsiveness (McCorkle et al., 1980). The response of mouse lymphocytes to mitogens in vitro was suppressed by permethrin at 20 μM (Stelzer and Gordon, 1984). That suppression showed little or no stereospecificity and was caused by both type I and type II pyrethroids, so it was suggested that it resulted from a nonspecific effect on membrane lipids. Permethrin also inhibited the mitogenic response of human lymphocytes to phytohemagglutinin in vitro (Diel et al., 1998). Feeding animals pyrethroids at high concentrations in long-term studies, however, did not cause an increase in infections (Ray, 1991). Cypermethrin has been reported to suppress humoral and cell-mediated immune responses in rats and rabbits directly (Dési et al., 1985). It was suggested that changes in the immune system constitute an early sign of mild exposure and could be an important part of early diagnosis (Dési et al., 1990).

Topical permethrin exposure might produce systemic immune effects. Thymic weight was reduced and splenic weight was increased with no change in body weight in mice by permethrin (at 0.5, 1.0, or 5.0 μL/day, which corresponds to topical insecticide application at about 22–220 mg/kg per day) applied to the shaved dorsal interscapular region

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daily for 10 or 30 consecutive days or every other day for seven or 14 exposures. Cell-surface-antigen expression did not change on thymocytes, splenocytes, or bone marrow cells, but the contact-hypersensitivity response was inhibited (Punareewattana et al., 2000). The splenic macrophage-chemiluminescent response was depressed 2 and 10 days after exposure. Phagocytic ability of macrophages was not inhibited. Antibody production, as demonstrated by a plaque-forming cell assay, decreased after 10 consecutive days of exposure (Punareewattana et al., 2001).

Hepatotoxic Effects

Granulomatous changes and giant cell infiltration in the liver have been observed in rodents and dogs experiencing acute fenvalerate intoxication (Okuno et al., 1986; Parker et al., 1984). Those changes, however, are thought to reflect a foreign-body response to deposition of crystals of a type of cholesterol, 2-(4-chlorophenyl)-isovalerate ester, in the liver (Miyamoto et al., 1986). The crystals are formed by microsomal carboxylesterases, and their formation is highly specific for fenvalerate (Kaneko et al., 1986, 1988).

Long-term treatment of rats and mice with pyrethroids produced a variety of liver changes, including increased liver weights (US EPA, 1988; Hallenbeck and Cunningham-Burns, 1985; Lehman, 1965); and microgranulomatous lesions (Kaneko et al., 1986; Okuno et al., 1986; Parker et al., 1983; Ray, 1991).

Other Health Effects

Blood glucose concentrations were increased by acute pyrethroid administration to rats; type II pyrethroids were more potent than type I pyrethroids (Cremer and Seville, 1982; Ray and Cremer, 1979). Thyroid weight was increased by chronic administration of resmethrin (US EPA, 1988). In addition, behavioral changes, decreased blood glucose concentrations, decreased body weights, and increased serum urea concentrations were noted in a 90-day resmethrin inhalation experiment with rats (US EPA, 1988).

Interactions with Other Agents

Piperonyl butoxide is a microsomal mixed-function oxidase inhibitor and has been used to increase the potency of pyrethroids by decreasing their metabolism (O'Brien, 1967). Inasmuch as some of the organophosphorous insecticides inhibit esterases and pyrethroids are hydrolyzed by esterases, synergism of the actions of pyrethroids and organophosphorous insecticides might pose a hazard.

Interactions have been seen between pyrethroids and DEET. Permethrin (15, 30 or 60 mg/kg), pyridostigmine (10 mg/kg), and DEET (50, 200 or 500 mg/kg) had little or no effect on the locomotor behavior of rats when given individually (Hoy et al., 2000a). Behavioral changes were seen, however, when two of them were applied concurrently. In males, the combination of permethrin and pyridostigmine affected speed, and permethrin and DEET affected speed and thigmotaxis. No effects were seen in female rats (Hoy et al., 2000a). Hoy and colleagues (2000b) also investigated open field locomotor activity. In males pyridostigmine and DEET decreased locomotor activity, but DEET in combination with permethrin increased locomotor activity. Females treated with pyridostigmine in combination with permethrin spent more time in the center zone of the open field locomotor activity area, indicating a decrease in thigmotaxis (Hoy et al., 2000b).

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The effects of concurrent exposure to pyridostigmine, permethrin, and DEET on multiple fixed-ratio and fixed-interval schedules of reinforcement in rats have also been studied (van Haaren et al., 2001). Exposure to either pyridostigmine or permethrin decreased fixed-ratio and fixed-interval response rates, and DEET decreased both response rates but only at the highest dose. Synergistic effects were observed only on fixed-interval response rate. Those rates were decreased after concurrent exposure to half the dose of pyridostigmine and half the dose of permethrin that alone affected fixed-interval response rate. The rates were also decreased after concurrent exposure to half the effective dose of pyridostigmine and half the effective dose of DEET. In addition, the permeability of the blood-brain barrier of the rat was unaffected by permethrin and slightly decreased by DEET but substantially reduced by a combination of the two (Abou-Donia et al., 2001).

LINDANE

Lindane belongs to a class of insecticides known as the organochlorines. Lindane is the γ-isomer of 1,2,3,4,5,6-hexachlorocyclohexane (HCH). The insecticidal activity of HCH was discovered in 1942.

Use of most organochlorine compounds has been banned since the 1970s in many countries, including the United States, because of their environmental persistence (such as DDT), their ability to bioconcentrate, and their biomagnification (Ecobichon, 2001). Lindane is used for treatment of ectoparasites on humans and animals, and it is used by humans as a lotion and a shampoo (Kwell®) (Facts and Comparisons, 2001; Woolley et al., 1985).

Chemistry

Technical HCH is comprised of four major isomers, α-, β-, γ-, and δ-HCH, in which the concentration of lindane (the γ-isomer) can range from 12 to 99%. Lindane is the most toxic of the isomers; its insecticidal activity is 28–10,000 times higher than that of the others (Ullmann, 1972). Although it is a misnomer, "benzene hexachloride" is a common name used in the United States for the mixture of HCH isomers. The structure of lindane is shown in Figure 3.4.

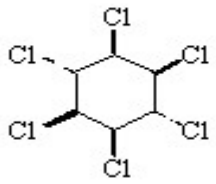

FIGURE 3.4 Structure of lindane.

Toxicokinetics

Lindane is rapidly absorbed from the gastrointestinal tract. It is much more slowly absorbed dermally (Dick et al., 1997). Once absorbed, it can be metabolized by dehydrogenation, dehydrochlorination, and hydroxylation in the liver. The metabolites of lindane are less acutely toxic than lindane, so those metabolic pathways are considered detoxification pathways (Fitzloff et al., 1982). It is excreted as glucuronide, sulfate, and mercapturic acid conjugates (Copeland et al., 1986).

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Mechanism of Action

In the cockroach, lindane evokes synaptic after-discharges and excessive release of acetylcholine (Shankland, 1979; Uchida et al., 1975). However, the major target site of lindane in mammals and insects is the γ-aminobutyric acid (GABA) receptor. GABA is the major inhibitory neurotransmitter in the brain. Activation of the GABA receptor opens chloride-ion channels in neurons. The GABA-induced chloride uptake that results from the channel's opening is inhibited by lindane (Ghiasuddin and Matsumura, 1982; Ogata et al., 1988). Lindane apparently interferes with binding to one subtype of GABA receptors, the $GABA_A$ receptors. Enhanced monoaminergic turnover has also been reported (Rivera et al., 1998), and central monoaminergic systems seem to have a role in lindane intoxication (Llorens et al., 1991).

Acute Human Exposures

Lindane has been used by humans to control scabies caused by mites and to combat lice in cream, ointment, emulsion, and aerosol formulations. Prescription products (Kwell® lotion and Kwell® shampoo) are available for human use (Facts and Comparions, 2001). Not many studies regarding lindane intoxication in humans have been published. A few cases of lindane intoxication following use for control of scabies were due largely to gross disregard of directions; it was applied to the entire body for many days or taken orally (Smith, 1991). A few deaths have been caused by accidental lindane ingestion, and there are many reports of nonfatal intoxication.

A large proportion of fatal and nonfatal lindane poisonings have been in children (Joslin et al., 1960; Savage et al., 1971). Accidental poisoning with lindane occurred when 11 people drank coffee prepared with lindane in place of sugar (Smith, 1991). Initial symptoms included malaise, faintness, and dizziness and were followed by collapse and convulsions, which were sometimes preceded by screaming and accompanied by foaming at the mouth and biting of the tongue. Nausea and vomiting occurred in many cases. The patients were unconscious during convulsions, and loss of consciousness lasted for 15 min to 3 h. Nine patients had retrograde amnesia. Most of the patients were discharged the next day.

Poisoning with lindane is often associated with the use of vaporizing devices. In two such cases, headache, nausea, and irritation of eyes, nose, and throat occurred shortly after exposure to vapors; the symptoms were reversible (AMA, 1952). Secondary effects seen following inhalation of lindane include blood dyscrasias, such as anemia, leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, thrombocytopenia, increased bone marrow megakaryocytes, and decreased bone marrow megaloblastoid of the erythroid series (Berry et al., 1987; Morgan et al., 1980), although Morgan and colleagues (1980) seriously questioned the role of lindane in blood dyscrasias.

Experimental Data

Neurotoxic Effects

Acute exposure of animals to lindane causes CNS stimulation, motor impairment, excitation, clonic (intermittent) and tonic (continuous) convulsions, increased respiratory rate or respiratory failure, pulmonary edema, and dermatitis (Drummer and Woolley, 1991;

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Smith, 1991). Appearance of tremors has not been reported. Lindane caused hypothermia and anorexia in rats (Aldegunde Villar et al., 1981; Camon et al., 1988; Woolley et al., 1985).

Repeated exposure of rats to subconvulsant doses of lindane led to persistent alterations in the CNS as evidenced by increased susceptibility to experimentally induced seizures (Gilbert, 1995). Repeated exposure to lindane also increased the number of errors in a food-reinforced maze; this suggested lindane interference with learning (Dési, 1974). Nonconvulsant doses of lindane were reported to interfere with the ability to acquire and use new information (Tilson et al., 1987).

Rivera and colleagues (1998) investigated the persistent effects of lindane (single or repeated dose) on motor activity. Rat pups were treated with lindane in a single dose (20 mg/kg) or for 7 days (10 mg/kg per day). Motor activity was tested on postnatal day 15. Acute lindane administration decreased motor activity, whereas repeated lindane administration increased motor activity. The authors suggested that the effect was due to an imbalance of the central monoaminergic and $GABA_A$ neurotransmitter system (Rivera et al., 1998).

Carcinogenicity

There is not complete agreement on the carcinogenicity of the chlorinated hydrocarbon insecticides, including lindane (Smith, 1991). A number of studies have been conducted on the carcinogenicity of lindane and technical-grade HCH, which contained lindane. Liver tumors and lung tumors were detected in mice fed diets that contained lindane at 12.5–600 ppm for 24–110 weeks (Hanada et al., 1973; Herbst et al., 1975; Ito et al., 1973a; Thorpe and Walker, 1973; Weisse and Herbst, 1977). Other researchers, however, reported no liver tumors in mice fed diets that contained lindane (100–500 ppm) for shorter periods (24–32 weeks) (Ito et al., 1973a,b; Nagasaki et al., 1972). Studies in rats fed lindane-containing diets did not detect an increase in tumors of any type, including liver tumors (Fitzhugh et al., 1950; Ito et al., 1975; NCI, 1977).

Mutagenicity

Data generally indicate that lindane and HCH are not mutagenic (Buselmaier et al., 1973; Lawlor et al., 1979; Probst al., 1981; Shahin and Von Borstel, 1977; Shirasu et al., 1976; Tsushimoto et al., 1983; Wildemauwe et al., 1983).

Reproductive and Developmental Effects

Reproductive studies of lindane have had mixed results. Although a low dose (5 mg/kg/day) of lindane had no effect on reproduction in rats, long-term administration of low doses (10 mg/kg/day for 138 days) of lindane reduced fecundity and litter size in one study (Trifonova et al., 1970). Dzierzawski (1977) reported an increase by a factor of 2–20 in the number of resorbed fetuses in hamsters, rabbits, and rats. In another study, a very low dose (0.5 mg/kg/day) of lindane increased the duration of diestrus, shortened the duration of estrus, lengthened the gestation period, decreased the number of fetuses, increased the number of dead fetuses, and decreased the growth of the young (Nayshteyn and Leybovich, 1971). Lindane given to rats by gavage on days 6–15 of gestation had no effect on the numbers of pregnancies, abortions, and dead or resorbed fetuses (Khera et al., 1979).

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Lindane also has been reported to cause the testes of rats to become atrophied. Seminiferous tubules and Leydig cells degenerated completely over a 10-day treatment period (8 mg/kg/day) (Chowdhury et al., 1987). The decreases in sperm production in mice treated with lindane for 8 months were reversible (Smith, 1991). Lindane also reduced "reproductive behavior" in young rams (Beard et al., 1999).

A number of studies indicate that lindane is not teratogenic. No birth defects were noted in the pups of beagles given lindane (7.5 or 15 mg/kg per day) from gestation day 5 through the end of gestation (US National Library of Medicine, 1995). A three-generation study of rats (Palmer et al., 1978) and experiments with mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984) also did not demonstrate any teratogenic effects. Rat offspring exposed to lindane via lactation were reported to have deficiencies that appeared in adulthood; the deficiencies included decreases in testicular weight, lowered number of sperm, and reduced testosterone production (Dalsenter et al., 1997). In utero exposure of rats to lindane reduced [^{35}S]t-butyl bicylcophosphorothionate (TBPS) binding in the brainstem, indicating a decrease in expression of $GABA_A$ receptors, but the clinical significance is unknown (Brannen et al., 1998).

Immunotoxic Effects

Weanling rats fed high doses of HCH for 90 days showed hypertrophy of the adrenals, reduction of steroidogenic enzymes, and accumulation of lipids that contain cholesterol (Shivanandappa et al., 1982). Immunosuppression was also reported (Descotes, 1986). Lindane given to weanling rats at low doses suppressed the humoral immune response to typhoid–paratyphoid vaccine (Dewan et al., 1980). Lindane in rats also suppressed the formation of an antibody against human serum albumin and at higher doses inhibited the uptake and lysis of bacteria by phagocytes (Rosival et al., 1974). Reduction of titers in an agglutination test was reported in cats that inhaled lindane and in rabbits that received it in their food (Burkatzkaya, 1963).

N,N-DIETHYL-3-METHYLBENZAMIDE (DEET)

N,N-Diethyl-3-methylbenzamide (*N,N*-diethyl-*m*-toluamide; DEET) has been on the worldwide market since the 1950s, and has proved to be an effective, broad-spectrum insect repellent. The compound was developed and patented by the US Army in 1946 for use by military personnel and was registered by US EPA in 1957 (US EPA, 1998). DEET can be applied directly to human skin and to clothing and other materials. It is also used on pets and livestock. It has been estimated that more than 30% of the US population uses DEET during insect-biting seasons. Its use reduces the incidence of vectorborne disease transmission, especially in tropical regions, and of insect bites.

Chemistry

The chemical structure of DEET is shown in Figure 3.5. The DEET in registered formulations must be at least 95% *meta*-isomer (Figure 3.5), but small amounts of the more toxic *ortho*-isomer and the less toxic *para*-isomer are permitted (Robbins and Cherniack, 1986). Formulations vary widely, but most products contain 10–25% DEET in alcohol.

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There are reports that military personnel are issued formulations containing up to 75% DEET.

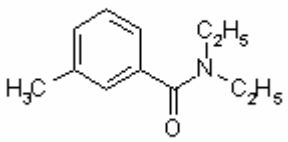

FIGURE 3.5 Structure of DEET.

Toxicokinetics

Topical application of DEET formulations results in accumulation of the repellent in skin layers. Penetration of the skin varies with the formulation, but studies in human volunteers suggest that less than 10% of an applied dose is absorbed. A much wider range of absorption rates has been reported in experimental animals than humans (Qiu et al., 1998). As with most organic compounds, percutaneous absorption would be expected to be greater in areas of skin damage.

DEET is detectable in human blood within 2 h of application to the adult forearm and was found to persist in the blood for at least 4 h (Selim et al., 1995). In rats, peak blood concentrations were achieved 1 h after skin application, and elimination was complete in 2–3 days (Schoenig et al., 1996). The compound and its metabolites are widely distributed in the body. Metabolites include carboxylic acids and hydroxymethyl compounds resulting from oxidation of the methyl group and loss of ethyl groups from the amide side chain (Qiu et al., 1998).

Genetic Polymorphisms and Susceptibility

No information specific to DEET is available on genetic polymorphisms.

Mechanism of Action

Little is known about the toxic mechanism of action of DEET.

Acute Human Exposures

DEET's overall safety record is good when it is used as directed in the labeling, but three deaths and 10 cases of encephalopathy (all cases except one were in children 8 years old and younger) have been reported to be associated with heavy, and sometimes even short-term, use of DEET formulations (Qiu et al., 1998). There have also been reports of seizures, mostly in children, from exposure to DEET. The national DEET registry (from 1960 to 1997) contains 14 cases of seizures potentially related to DEET for which other more likely causes have not been identified and another 32 cases under review to determine whether there are other more likely causes. In a summary prepared for the reregistration of DEET, US EPA (1998) estimated, on the basis of those data, an incidence of seizures of about one per 100 million users. Reports of acute manic psychosis, cardiovascular toxicity, and anaphylaxis are limited to single, isolated cases, but dermatitis, urticaria, and other skin effects have been more commonly reported (Qiu et al., 1998). Veltri and colleagues (1994) summarized 9086 cases of human exposures to DEET products that had been reported to poison control centers in 1985–1989. The largest fraction (32%) of the cases were related to ocular symptoms, including corneal abrasion, resulting from accidental spraying of products into the eyes. It was possible to follow the course of injury in 24.8% of cases; in 98% of the cases that were followed, there were no long-term sequelae (Veltri et al., 1994).

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No other important adverse effects resulting from DEET have been reported in humans. One study of 249 US Gulf War veterans, however, provides evidence of an association between the frequency and amount of skin application of a repellent containing 75% DEET and the risk of a set of symptoms characterized as "arthro-myo-neuropathy" (Haley and Kurt, 1997). Contact dermatitis and urticaria were also reported in some people who used that formulation (Haley and Kurt, 1997).

Experimental Data

Neurotoxic Effects

A single dose of DEET at 1 or 3 g/kg produced neurotoxicity and neuropathy in rats. Many animals recovered fully, a few remained ataxic, others failed to recover muscle tone or righting reflex over 24 h, and some died. Some animals were killed between 2 h and 8 days after treatment for pathologic assessment. Intramyelinic edema, evident from the earliest time, evolved into a patchy and reversible spongiform myelinopathy largely in the cerebellar roof nuclei. Animals that had long-lasting prostration and partially controlled motor seizures displayed scattered neurons with edematous clefts of uncertain origin and significance (Verschoyle et al., 1992). Those findings provide insight into the possible target or mechanism underlying acute DEET-associated encephalopathy.

In subchronic and chronic repeat-dose studies involving dietary administration of DEET to mice, rats, and rabbits, the only consistent effects observed were decreased body weight gain; increased relative weights of testes, liver, and spleen; and increased serum cholesterol (Schoenig et al., 1999). No evidence of an effect on animal survival or abnormal findings of hematology, urinalysis, or gross or microscopic pathology were reported in any dose group. In dogs, tremor, hyperactivity, emesis, excessive salivation, and slightly reduced hemoglobin and hematocrit were reported at oral doses of 400 mg/kg per day given for 1 year; no effects were seen at 100 mg/kg per day (Schoenig et al., 1999).

Schoenig and colleagues (1993) investigated the neurotoxicity of DEET in rats following acute gavage exposure and following multigenerational dietary exposure. Effects on a functional observational battery (FOB) and motor activity measurements were studied following the acute exposure. In addition to the FOB and motor activity tests, an M-maze, passive avoidance acquisition and retention tests, acoustic-startle habituation, and histologic outcomes were also assessed in the multigenerational study. Other than a slight decrease in motor activity at 5000 ppm in the feeding study (rats taken from the second generation of a two-generation study), no evidence of adverse effects was seen.

Reproductive and Developmental Effects

An early study (Gleiberman et al., 1975) reported increased prenatal mortality and some effects on reproductive measures in rats at a maternal dose of 1000 mg/kg per day (dermal). Little evidence of effects on reproduction or development, however, was seen in studies in rats (two studies by the dermal route, one by gavage) and in rabbits (one study by the dermal route, one by gavage) (Schoenig et al., 1994). Another more recent study also did not confirm the findings of Gleiberman and co-workers (1975).

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Interactions with Other Agents

The toxicity of DEET coadministered with organophosphorous compounds or permethrin has been investigated to understand toxicosis in domestic cats treated for fleas and ticks. Such research has also been conducted to explore hypotheses related to unexplained illness among US forces in the Gulf War, many of whom used the anticholinesterase drug pyridostigmine bromide (PB) prophylactically against possible nerve-agent exposure in addition to DEET.

Dermal exposures to DEET and at least one pyrethroid have demonstrated unexpected toxicity in cats. Hypersalivation, ataxia, depression, seizures, and death occurred in cats within 4–6 h of dermal application of DEET and fenvalerate (Dorman et al., 1990).

Two laboratories have reported studies in hens and rats demonstrating that various binary and tertiary combinations of PB, DEET, permethrin, and chlorpyrifos produced greater neurotoxicity than the same compounds administered individually at comparable doses (Abou-Donia et al., 1996; van Haaren et al., 2001). Effects on locomotion and thigmotaxis have been reported for combinations of DEET with PB or permethrin. All the studies that showed increased toxicity involved subcutaneous or intravenous (rather than dermal) administration of at least one of the compounds involved.

Increased permeability of the blood-brain barrier and the blood-testis barrier has been reported in rats exposed dermally to DEET and permethrin for 60 days (Abou-Donia et al., 2001). Milder effects were reported for DEET alone, but not for permethrin alone. It is not possible to evaluate the relevance of those experimental findings to humans except to note toxicity may be increased by some combinations of the substances under the specific experimental conditions used.

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4

SOLVENT TOXICOLOGY

Solvents are a heterogeneous group of thousands of chemical compounds that can dissolve other chemicals (Rosenberg et al., 1997). That property makes them useful in occupational and home settings for a variety of purposes, including cleaning and degreasing; a few hundred of them have found use as commercial products, many as degreasing agents in industrial settings. Water is the most common solvent, and many solvents are water-based. Non-water-based, or organic, solvents are hydrocarbon-based and lipophilic and therefore are able to extract, dissolve, or suspend fats, oils, and waxes.

Although Congress identified the specific insecticides for study in the legislation on Gulf War exposures, it did not identify the solvents that should be examined by the committee. The committee itself identified a large number of solvents sent to the Gulf War (Chapter 1 and Appendix D), many of which have been extensively studied experimentally.

In light of the large number of solvents sent to the Gulf War and because the toxicity data are used only for background information and supportive evidence (Chapter 2), an extensive review of toxicologic studies of solvents is not appropriate here. Instead, this chapter begins with a review of the general chemistry and toxicokinetics of solvents, the effects of exposure to solvents as a general class, and general interactions that might occur between solvents and other chemicals. Those sections are followed by information on some groups of organic solvents that have unique toxicologic properties or effects or that warrant special mention because of their use in the Gulf War: the aromatic hydrocarbons, halogenated hydrocarbons, alcohols, glycols, glycol ethers, esters, ketones, and petroleum distillates.

It should be noted that data on the solvents discussed here have been reviewed elsewhere—for example, by the Agency for Toxic Substances and Disease Registry, the World Health Organization, the International Agency for Research on Cancer, and the Environmental Protection Agency and in chapters in toxicology textbooks (e.g., Bruckner and Warren, 2001). The reader is referred to those sources for more detailed reviews of the experimental and human data on the various solvents.

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GENERAL SOLVENT INFORMATION

Toxicokinetics

The lipophilicity of many organic solvents facilitates their absorption after inhalation or oral or dermal exposure (Bruckner and Warren, 2001). Because of their volatility, the major route of occupational exposure to solvents is inhalation, although dermal exposure can be important in some cases. Once it is absorbed, the disposition and metabolism of a solvent are affected by the route of exposure and by its chemical and physical properties. After ingestion, metabolism and elimination can occur in the first pass through the liver and lungs, before the compound reaches the systemic circulation. Following inhalation exposure most solvents are absorbed rapidly and extensively into the pulmonary and arterial circulation. Some solvents are metabolized to less toxic compounds, others to more toxic compounds or toxic intermediates. Regardless of the route of exposure, unmetabolized lipophilic solvents are distributed predominantly to fatty tissues. Water-soluble solvents, such as alcohols are an exception; they are distributed with body water. Generally, the solvents used in the Gulf War are not highly persistent in the body and are eliminated in a matter of days once exposure ceases.

Toxicity

The central nervous system (CNS) is a major target of organic solvents (Bruckner and Warren, 2001). The CNS-depressing effects of acute, high-dose exposure to solvents are well established in humans and animals, and exposure to most solvents can lead to narcosis if the dose is high enough. In addition, most organic solvents are mucous-membrane irritants and dermal irritants, but only following repeated or prolonged dermal exposure to high concentrations. Permanent CNS damage can occur in humans who chronically abuse solvents, but the effects of low-dose exposure to solvents are less clear. The data on low-dose exposures to solvents come primarily from the epidemiologic literature, which is discussed in the health-outcomes chapters, Chapters 5–9.

In addition to the general chronic solvent-induced CNS effects, some solvents (for example, *n*-hexane, carbon disulfide, and methyl *n*-butyl ketone) cause peripheral neuropathy (Graham et al., 1995); symptoms of subchronic and chronic exposure, appear insidiously over weeks to months. The specific solvents known to produce peripheral neuropathy are not believed to have been sent to the Gulf War and are not examined in Chapters 5–9. The clinical features of the neuropathy include sensory loss, distal weakness, and areflexia with a slowing of motor conduction velocity. Nerve biopsy shows axonal degeneration with neurofilamentous axonal swelling and axonal atrophy. Symptoms can progress for months after exposure stops (Huang et al., 1989). In milder cases, symptoms eventually resolve; in more severe cases, residual disability persists over the long term (Arlien-Sobørg, 1992; Feldman, 1998). To judge by the onset and the clinical course, peripheral neuropathy from solvent exposure is a long-term effect. Such peripheral neuropathy was first recognized in humans exposed in the occupational setting and later verified in experimental animals. Peripheral neuropathy is also seen in persons who abuse solvent products containing *n*-hexane or methyl-*n*-butyl ketone. *N*-hexane, carbon disulfide, and methyl-*n*-butylketone produce identical pathologic and clinical changes. The neurotoxicity of *n*-hexane and methyl-*n*-butylketone was found to be mediated by a common

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metabolite, 2,5-hexanedione. In contrast, carbon disulfide does not share that metabolite and does not require metabolism for its toxicity. Review of the solvents sent to the Gulf War provides no evidence that military personnel were exposed to *n*-hexane, methyl-*n*-butyl ketone, or carbon disulfide. Furthermore, none of the solvents used in the Gulf War is expected to be neurotoxic through a mechanism similar to that of *n*-hexane, because none of them has a γ-diketone metabolite thought to be required to produce an "*n*-hexane-like" neuropathy.

Interactions

In most settings, exposures occur to mixtures of solvents (Bruckner and Warren, 2001). Because many solvents have a common mechanism of action for some outcomes (for example, CNS depression), there can be additive effects. Some solvents (such as ethanol) can induce metabolic enzymes. Those enzymes can catalyze the metabolic activation of some solvents and the metabolic detoxification of others. Therefore, the induction of those enzymes can lead to a potentiation of the toxicity of some solvents and reduce the magnitude and duration of the toxicity of other solvents. Interactions can also occur between compounds that have similar toxic outcomes (for example, carbon tetrachloride and chloroform and their effects on the liver).

Genetic Polymorphisms and Individual Susceptibility

Numerous genetic polymorphisms in metabolic enzymes can alter the toxicokinetics, and consequently the toxicity, of solvents that they metabolized (Bruckner and Warren, 2001; Löf and Johanson, 1998). People who take medications or are exposed to other chemicals that affect those enzymes might have altered susceptibility to some solvents, and people with such conditions as liver disease or kidney disease might be more susceptible to the toxicity of solvents.

AROMATIC HYDROCARBONS

Aromatic hydrocarbons are a class of compounds that contain an unsaturated ring structure (Bruckner and Warren, 2001). Benzene, toluene, and xylenes are aromatic hydrocarbons that were or are widely used as solvents and that are thought to have been sent to the Gulf War (see Figure 4.1 for structures). Although no longer used widely as a general-purpose solvent because of concerns about its toxicity, benzene is still used in the synthesis of other chemicals and is a component of gasoline and JP-8 jet fuel. The metabolism of benzene, which occurs in the liver and to a lesser extent in the bone marrow, plays an important role in its toxicity. Benzene is metabolized to benzene oxide, an epoxide, through an oxidation reaction catalyzed primarily by cytochrome P450 2E1. Cytochrome P450 2E11/6 also participates in benzene biotransformation. Benzene oxide can then be metabolized to various compounds, including *o*-benzoquinone and *p*-benzoquinone, which are thought to be the two main metabolites that mediate the toxicity of benzene.

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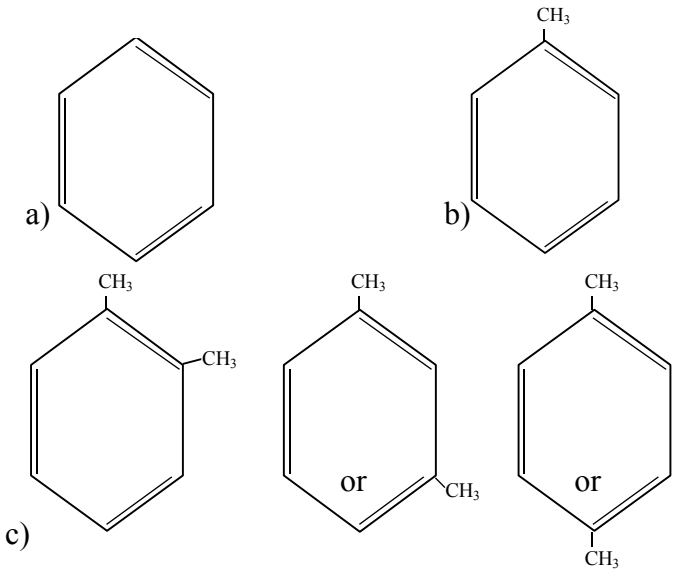

FIGURE 4.1 Structure of a) benzene, b) toluene, and c) xylenes.

Data from laboratory animals and humans show that benzene affects the bone marrow in a dose-dependent manner, causing anemia, leukopenia, and thrombocytopenia; continued exposure causes aplasia and pancytopenia (Bruckner and Warren, 2001). Benzene also has carcinogenic properties. In experimental animals, an increased incidence of malignant lymphomas and some solid tumors have been seen after exposure to high doses of benzene. As discussed in Chapter 6, benzene has also been associated with some types of leukemia in humans. Differences in cancer sites among species indicate that species differences in the carcinogenicity of benzene exist.

Because of the health concerns associated with benzene, it has been replaced in many uses with other solvents, especially toluene and xylenes (Bruckner and Warren, 2001). Toluene and xylenes are widely used in the production of other chemicals and, like benzene, are components of gasoline. Toluene is also present in paints, thinners, cleaning agents, and glue and is widely abused as an inhalant. Toluene and xylenes have the same general toxicity as many solvents, but animal data do not indicate that they are hematopoetic toxicants; the tumors associated with exposure to benzene do not appear to be associated with exposure to toluene and xylenes. Auditory toxicity has been demonstrated in animals following toluene exposure. In rats, intermediate exposures (1000 and 1200 ppm for 14 hours/day for 2 to 9 weeks) resulted in permanent loss of hearing in the high frequency range. A loss of hair cells has been seen following exposure to auditory-toxic concentrations of toluene and could be involved in the underlying mechanism (ATSDR, 2000). Toluene and xylenes are methylated benzenes and, unlike benzene, are metabolized at the methyl group(s) and then readily eliminated.

HALOGENATED HYDROCARBONS

Halogenated hydrocarbons contain at least one halogen atom (such as chlorine, bromine or fluorine). Four halogenated hydrocarbons are discussed in this section: tetrachloroethylene, trichloroethylene, methylene chloride, and chloroform.

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Tetrachloroethylene

Tetrachloroethylene (perchloroethylene) is one of the most widely used chlorinated solvents. It is used in dry cleaning and as a degreaser, and it is a component of water repellents, heat-exchange fluids, grain fumigants, and typewriter correction fluids (Bruckner and Warren, 2001).

There is evidence that tetrachloroethylene is carcinogenic in animals (Bruckner and Warren, 2001). An increased incidence of mononuclear-cell leukemia was observed in male and female Fischer 344 rats exposed to tetrachloroethylene. Renal tubular cell adenomas and adenocarcinomas, which are rare in untreated male rats, were observed in male rats exposed to tetrachloroethylene. Oral exposure of male and female mice to tetrachloroethylene over a lifetime resulted in a dose-dependent increase in the incidence of hepatocellular carcinomas.

Tetrachloroethylene's ability to cause liver tumors in mice appears to be mediated by trichloroacetic acid, its major metabolite (ATSDR, 1997a). Trichloroacetic acid can induce peroxisome proliferation in mice, which can apparently play a role in liver cancer in B6C3F1 mice (Bull, 2000). Trichloroacetic acid induces peroxisome proliferation to a much lesser extent in rats and does not lead to liver cancer in rats (Bull, 2000). Data indicate that humans are relatively insensitive to peroxisome proliferators (Cattley et al., 1998) and produce only very small amounts of trichloroacetic acid after tetrachloroethylene exposure (ATSDR, 1997a). Therefore, that mechanism of liver carcinogenesis in rodents might not be relevant to humans exposed to tetrachloroethylene (Cattley et al., 1998). Another mechanism proposed to underlie the toxicity of tetrachloroethylene is the production of a reactive epoxide intermediate in the metabolism of tetrachloroethylene to trichloroacetic acid (ATSDR, 1997a).

The renal carcinogenesis observed in a low incidence in male rats may occur, in part, from the conjugation of tetrachloroethylene with glutathione in the liver, followed by the formation of genotoxic metabolites in the kidney by β-lyase (Bruckner and Warren, 2001). That glutathione metabolite is formed in substantially smaller amounts in humans (Volkel et al., 1998). It could, nevertheless, play a role in renal carcinogenesis in humans exposed chronically to very high concentrations of tetrachloroethylene. Another mechanism that might underlie the renal toxicity of tetrachloroethylene in male rats, the accumulation of α-2μ-globulin, is also not relevant to humans, because humans do not produce α-2μ-globulin or related proteins in quantities of concern (Green et al., 1990).

Trichloroethylene

Trichloroethylene is a common environmental contaminant that is used as a degreaser, in textile processing, and as an extraction solvent. Trichloroethylene is found in common consumer products, such as typewriter correction fluids, paint removers and strippers, adhesives, spot removers, and rug-cleaning fluid (Bruckner and Warren, 2001).

Most absorbed trichloroethylene is oxidized by hepatic cytochrome P450s to chloral hydrate, trichloroethanol, and trichloroacetic acid (Bruckner and Warren, 2001). Trichloroethylene when inhaled or ingested has been shown to induce liver cancer in B6C3F1 mice but not in rats. That species difference is thought to be due largely to the greater oxidative metabolism of trichloroethylene in mice than in rats. The carcinogenicity of trichloroethylene is mediated largely by trichloroacetic acid and dichloroacetic acid (a minor metabolite), which are thought to contribute to an increase in liver cancers by

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inducting peroxisome proliferation. As discussed previously, that mechanism of carcinogenesis might not be relevant to humans (Cattley et al., 1998). In addition, trichloroacetic acid and dichloroacetic acid decrease the rate of normal hepatocyte replication, conferring a selective growth advantage to initiated tumorigenic cells (an example of "negative selection"). Another effect of trichloroacetic acid and dichloroacetic acid that might be related to liver carcinogenicity is the stimulation of DNA replication in hepatocytes. That effect, however, manifests only at very high concentrations (Bull, 2000). Trichloroethylene at low doses also increases renal tubular cell adenomas in male rats.

Inhaled trichloroethylene is a respiratory carcinogen in mice but not in rats (Bruckner and Warren, 2001). Chloral hydrate is the metabolite primarily responsible for pulmonary tumor formation. Clara cells, which have high P450 activity to metabolize trichloroethylene, are much more numerous in the mouse lung than in the lungs of rats and other animals. The human lung has very few Clara cells. They are the primary target of trichloroethylene in the mouse lung (Green, 2000). Toxicity to Clara cells is characterized by vacuolization, necrosis and an increase in cell replication. Inhalation of trichloroethylene in rats has also resulted in increased leukemias and Leydig cell tumors. Male rats exhibited a dose-related increase in Leydig cell tumors and a slight increase in tubular renal adenocarcinomas.

Methylene Chloride

Methylene chloride is used as an extractant for fats and paraffins in the food and pharmaceutical industries and as a postharvest fumigant for grains and strawberries. It was used in hair sprays until 1989 (FDA, 1989) and was used to remove caffeine from coffee.

Exposure to methylene chloride is of concern primarily because of its potential as a human carcinogen, in light of its carcinogenicity in rodents. Evidence suggests that oral exposure to methylene chloride increases the incidence of liver cancer. Acute exposure to methylene chloride induces ornithine decarboxylase in laboratory animals, which is indicative of the promotion of liver cancer (Kitchin and Brown, 1989). Chronic high exposure to methylene chloride in laboratory animals, particularly mice, results in an increase in lung adenomas or carcinomas. Increased numbers of salivary gland sarcomas have been seen in male rats (Burek et al., 1984) and benign mammary tumors in female rats (Burek et al., 1984; Mennear et al., 1988; Nitschke et al., 1988) after exposure to high concentrations of methylene chloride vapors. An increased incidence of lung tumors, but not liver tumors, was seen.

Genotoxic end points have been observed in mice and rats and their tissues after methylene chloride exposure. There has been a great deal of research to define mechanisms underlying the carcinogenicity of methylene chloride, so that the relevance of the murine tumors to humans can be understood (Green, 1997). Liver and lung tumors in mice do not seem to be associated with overt cytotoxicity or increased replicative DNA synthesis (Maronpot et al., 1995). Induction of the tumors is generally believed to be due to a reactive intermediate generated by the glutathione-*S*-transferase (GST) pathway (Andersen et al., 1987). The theta class GST isozyme GST T1-1 catalyzes the conversion of methylene chloride to *S*-chloromethylglutathione in the liver and lung, which appears to break down rapidly to glutathione and formaldehyde. The formation of this unstable intermediate occurs in the proximity of DNA in mice and results in single-strand DNA breaks that could play a role in the development of cancer.

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An alternative mechanism has been suggested to underlie the carcinogenicity of methylene chloride. Casanova and colleagues (1997) proposed that formaldehyde, a metabolite of methylene chloride, causes the formation of DNA–protein cross-links. When hepatocytes from humans and from several other species were incubated with methylene chloride, DNA–protein crosslinks were found only in the mouse samples. That suggests that mice are more susceptible than other species to the carcinogenic effects of methylene chloride.

Chloroform

Chloroform was introduced in 1847 as an inhalation anesthetic (Bruckner and Warren, 2001). It is no longer used as an anesthetic in humans, but it is used in some endodontic procedures and in the administration of drugs for the treatment of some diseases. It is used in the production of chemicals, as an extraction solvent, as a heat-transfer medium in fire extinguishers, and as an intermediate in the preparation of dyes and pesticides.

The metabolism of chloroform (Figure 4.2) is important to its toxicity, because its toxicity is mediated by reactive metabolites that bind to macromolecules (lipids and proteins) of the endoplasmic reticulum. Most chloroform metabolism occurs by oxidation.

A primary target of chloroform is the liver, and liver necrosis is one of the major toxic effects that has been observed in humans and animals after inhalation and oral exposure to high doses of chloroform (Bruckner and Warren, 2001). Leakage of cytoplasmic liver enzymes into the bloodstream, increases in liver triglycerides, and decreases in liver reduced-glutathione levels have been seen in rodents after exposure to chloroform. Other effects seen in rats and mice are centrilobular hepatocyte necrosis, vascular degeneration in midzonal and periportal portions of the liver lobule, and a decrease in the eosinophilia of the centrilobular and midzonal hepatocyte cytoplasm, acute hepatitis, increased liver weights, and diffuse centrilobular swelling.

The kidneys are another major target of chloroform after both inhalation and oral exposure (Bruckner and Warren, 2001). Tubular necrosis, increased kidney weight, increased cell proliferation, and epithelial cell lesions in the proximal convoluted tubules have been seen in mice after inhalation exposure to chloroform. Tubular necrosis, tubular swelling, and increased kidney weight have occurred in rats after oral exposure.

Liver and kidney tumors have also been seen in animals after exposure to chloroform; the tumors depend on the species, strain, and sex of the animal and on the dosage of chloroform (Bruckner and Warren, 2001). Inhalation exposure to chloroform in BDF1 male mice resulted in renal tubular tumors (Nagano et al., 1998). Exposure to chloroform in drinking water resulted in increased hepatic neoplastic nodules in female Wistar rats and adenofibromas in male and female Wistar rats (Tumasonis et al., 1987). Oral exposure studies indicate a dose-related increase in hepatocellular carcinomas in both male and female mice receiving chloroform in corn oil by gavage (NCI, 1976). An increase in renal tumors was seen in male rats receiving chloroform by gavage (tubular adenoma and carcinoma) (NCI, 1976) and in drinking water (renal tubular adenomas and adenocarcinomas) (Jorgenson et al., 1985). Male mice, but not female mice or male and female rats, demonstrated an increase in renal tumors following exposure to chloroform in a toothpaste base (Palmer et al., 1979; Roe et al., 1979). Those carcinogenic effects, however, occur only at high doses. The nonlinearity of the relationship between chloroform dose and tumor formation is consistent with the evidence that chloroform is not genotoxic. The

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carcinogenic effects are thought to be associated with regenerative hyperplasia that is in response to cell death and the data suggest that human exposures do not cause hyperplasia, and therefore would not result in carcinogenesis (Bruckner and Warren, 2001).

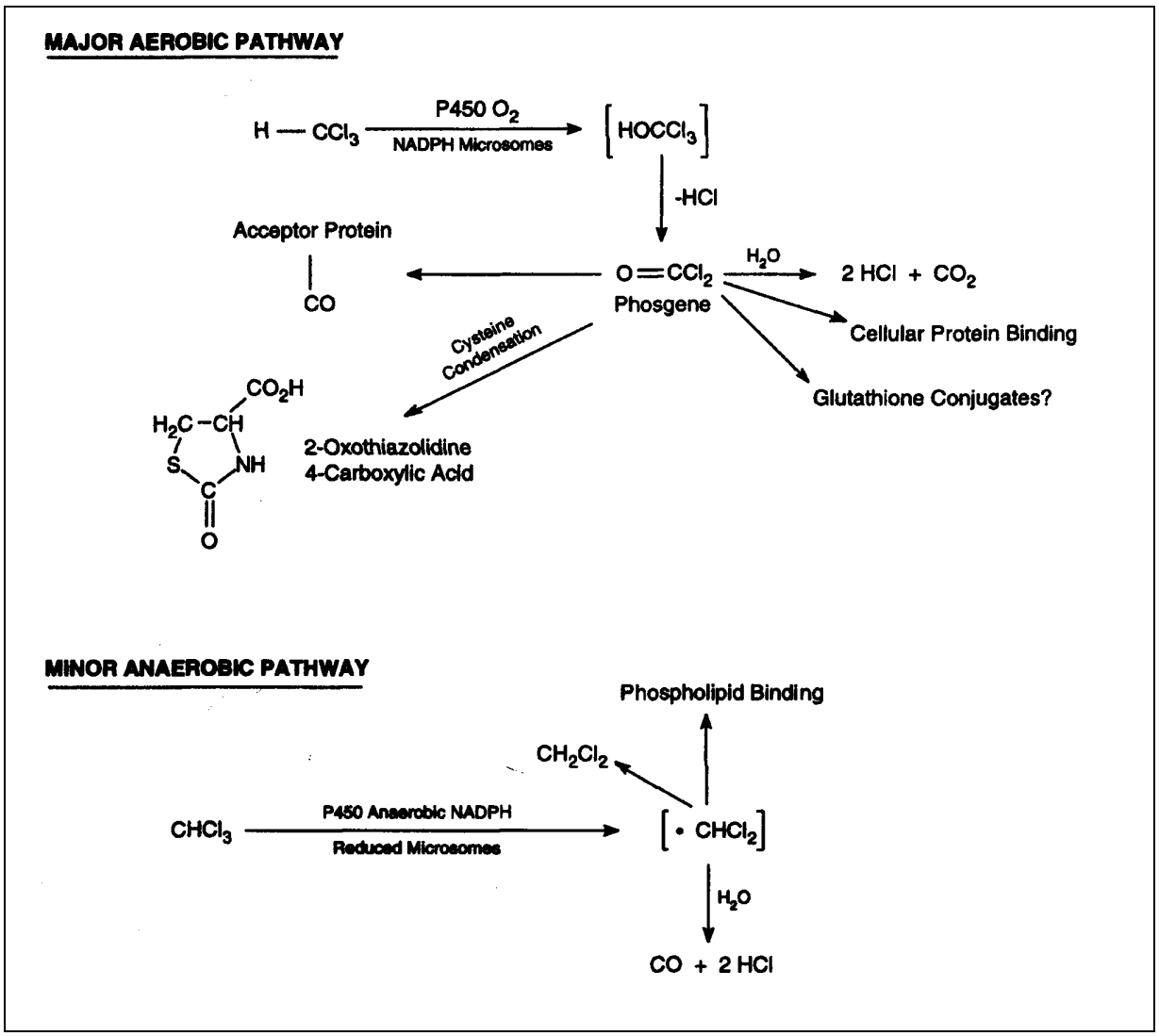

FIGURE 4.2 Metabolic pathways of chloroform biotransformation.

SOURCE: ATSDR, 1997b.

ALCOHOLS

Alcohols are widely used solvents that elicit the general solvent effects discussed earlier. Figure 4.3 shows the chemical structures of four representative alcohols: two primary aliphatic alcohols, methanol and ethanol; one secondary aliphatic alcohol, isopropanol; and one cyclic secondary alcohol, cyclohexanol.

In addition to CNS depression, methanol exposure in primates results in serious effects mediated by metabolites. Methanol can produce severe acidosis and retinal damage

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in primates by the production of its metabolite formate at exposures that do not produce substantial CNS depression (ATSDR, 1993; Tephly, 1991); these effects occur after high-dose exposure. Considerable differences exist among species in the capacity of their folate-dependent one-carbon pool to metabolize formate. In nonprimates, formate is metabolized rapidly; in primates, it is metabolized slowly and accumulates, leading to metabolic acidosis and ocular damage. The relative deficit in formate metabolism in primates has been attributed to lower tissue folate concentrations. It is consistent with that hypothesis that nonprimate laboratory animals fed a folate-deficient diet demonstrate sensitivities to methanol that are similar to those seen in primates (Tephly, 1991; Valentine, 1990). Methanol-induced ocular lesions are characterized by a loss of retinal ganglion cells, retinal edema, and demyelination of the temporal retina. Necrosis of cells with or without hemorrhage in the basal ganglion and widespread hypoxia/ischemic damage are also associated with methanol intoxication. At low doses, however, the formate detoxification pathway is not overwhelmed, and formate does not build up.

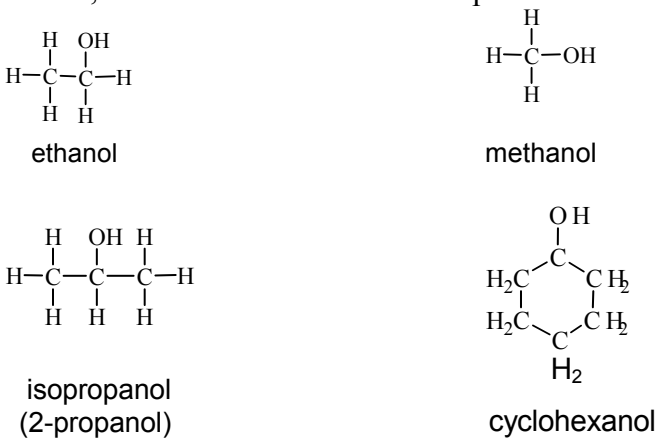

FIGURE 4.3 Structure of various alcohols.

Administration of cyclohexanol to male gerbils and rats by subcutaneous injection (15 mg/kg/day) for 21 and 37 days, respectively, was associated with reproductive toxicity (Tyagi et al., 1979). The adverse effects observed included decreased weights of the testes, epididymis, seminal vesicles, and ventral prostate and degenerative changes in spermatozoa and spermatozoa precursors. Similar changes in the testes were seen in rabbits given cyclohexanol by gavage (25 mg/kg/day) for 40 days (Dixit et al., 1980). In contrast, no change in testicular weights was observed in Sprague Dawley rats given cyclohexanol by gavage (455 mg/kg/day) for 7 days (Lake et al., 1982).

Ethanol can elicit a wide array of serious adverse effects when ingested, but it is unlikely that such effects are associated with the internal doses likely to result from inhalation.

GLYCOLS

Glycols, which are characterized by the presence of two hydroxyl groups (see Figure 4.4 for structures), are major constituents of antifreeze, airplane deicers and anti-icers, brake fluids, and heat exchangers. Propylene glycol is used in cosmetics and foods and as a vehicle for drug delivery.

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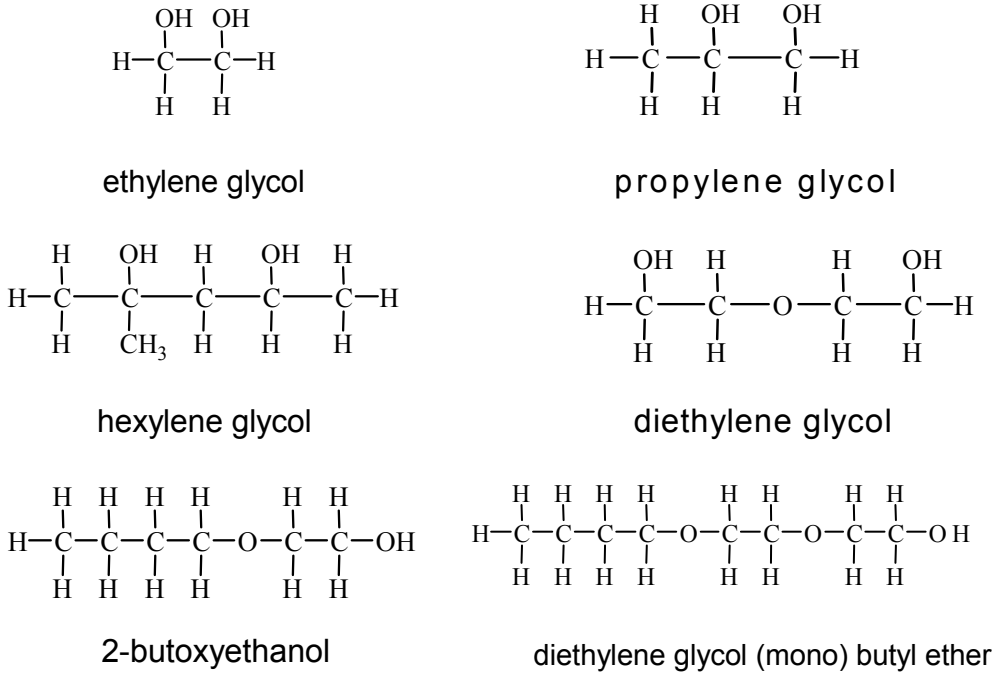

FIGURE 4.4 Structure of various glycols.

Ethylene glycol, propylene glycol, diethylene glycol, and hexylene glycol differ greatly in their potential to produce acute or chronic toxicity (ATSDR, 1997c; BIBRA, 1991, 1993; Lakind et al., 1999; Ruddick, 1972; Snyder and Andrews, 1996). Glycols are metabolized through successive oxidative steps, and the resulting metabolites account for the observed differences in toxicity among the glycols (ATSDR, 1997c; Lakind et al., 1999; Ruddick, 1972; Snyder and Andrews, 1996). Propylene glycol, which is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to lactate, that can be used in gluconeogenesis, has low toxicity. The principal metabolic pathway for ethylene glycol proceeds through glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid. The rate-limiting step in this pathway is the oxidation of glycolic acid to glyoxylic acid. As a result, substantial concentrations of glycolic acid accumulate. The buildup of glycolic acid is thought to be a major factor in the metabolic acidosis involved in the toxicity of ethylene glycol.

Renal toxicity of ethylene glycol or diethylene glycol has been observed in experimental animals (including rodents, primates, canines, and felines) after oral, dermal, and inhalation exposure (ATSDR, 1997c; Lakind et al., 1999; Snyder and Andrews, 1996). The renal lesions produced are similar among species, but humans and cats are 2–5 times more sensitive than rodents and dogs. The lesions observed include renal tubular epithelial degeneration and necrosis. The clinical signs associated with the renal toxicity include polyuria, anuria, crystaluria, and oliguria.

The mechanism of renal toxicity is a matter of debate, and several contributing mechanisms have been proposed (Lakind et al., 1999). The oxalic acid metabolite chelates calcium, generating calcium oxalate, which precipitates in numerous organs. Hypocalcemia

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may ensue, with the potential to exacerbate cardiovascular effects produced by the metabolic acidosis. Deposits of calcium oxalate crystals in the renal interstitium have been proposed as contributing to renal dysfunction through physical damage and blockage of the tubules. Evidence has also been presented that other acid metabolites, including glycolic acid and glyoxylic acid, contribute to renal toxicity through direct cytotoxic effects on the renal tubular epithelium. Frantz and colleagues (1996) demonstrated that differences in the metabolism and kinetics of ethylene glycol between mice and rats are related to the differential susceptibility of the two species to ethylene glycol. Metabolic acidosis and an increased osmolal gap may also contribute to renal toxicity by altering intracellular osmotic pressure.

Diethylene glycol shares with ethylene glycol the ability to produce renal toxicity (BIBRA, 1993; Snyder and Andrews, 1996). In contrast with ethylene glycol, however, it does not produce metabolic acidosis or calcium oxalate crystals. The observation that diethylene glycol produces identical lesions and is a more potent nephrotoxicant has been presented to support the contribution of non-oxalic acid metabolites to glycol-mediated nephrotoxicity.

GLYCOL ETHERS

Glycol ethers are used extensively in consumer products, including paints and textile dyes; as an anti-icer in brake fluids; and as a gasoline additive (Bruckner and Warren, 2001). This section discusses ethylene glycol monomethyl ether (EM), ethylene glycol monoethyl ether (EE), propylene glycol monomethyl ether (PM), and ethylene glycol monobutyl ether (EB) (see Figure 4.5 for structures).

a)

$$R—OCH_2CH_2OH \rightarrow R—OCH_2COOH$$

(where, R = CH_3 for EM; CH_3CH_2 for EE; and $CH_3CH_2CH_2CH_2$ for EB)

b)

$$R—OCH_2—\underset{CH_3}{CHOH} \rightarrow HO—\underset{CH_3}{CH_2CHOH}$$

(where R = CH_3 for PM; CH_3CH_2 for PE; and $CH_3CH_2CH_2CH_2$ for PB)

FIGURE 4.5 Structure of glycol ethers and their metabolites.

a) ethylene glycol ethers, and b) propylene glycol ethers. Abbreviations: EM, ethylene glycol monomethyl ether; EB, ethylene glycol monobutyl ether; PM, propylene glycol monomethyl ether; PE, propylene glycol monoethyl ether; PB, propylene glycol monobutyl ether.

Although ingestion of glycol ethers is not acutely hazardous, reproductive toxicity and teratogenicity are of concern in connection with some of them (Bruckner and Warren,

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2001). High exposures to EM and EE cause testicular atrophy and a decrease in white blood cells in mice. Treatment of rabbits and rats for 13 weeks with EM caused degeneration of testicular germinal epithelium and infertility; partial recovery was seen after 13 weeks. Exposure of pregnant rats to EE for 7 h/day on gestational days 7–15 caused fetal death with no signs of maternal toxicity. Cardiovascular and skeletal malformations were seen. Cardiovascular malformations have also been seen in the offspring of pregnant rabbits exposed to EE.

Exposure to PM, however, is not associated with reproductive or teratogenic effects (Bruckner and Warren, 2001). The differences in toxicity between PM and the other glycol ethers appear to be due to differences in their metabolism. Evidence indicates that the toxic effects of EM, EE, and EB are mediated by alkoxyacid metabolites (for example, methoxyacetic acid is a metabolite of EM). In contrast, the nontoxic PM does not have an alkoxyacid metabolite; it is metabolized to propylene glycol.

ESTERS

Organic esters are produced by the condensation of an alcohol and carboxylic acid with removal of water (see Figure 4.6 for structures of esters). The chemical properties of the ester depend on the structure of its alcohol and acid moieties. The two esters of potential concern in this document, because of their use in the Gulf War, are butyl acetate, an aliphatic ester, and 1-methoxy-2-propanol acetate, a propylene glycol ether ester. Butyl acetate is used as a flavoring agent and a solvent for cosmetics, lacquers, and adhesives. 1-Methoxy-2-propanol ether acetate (propylene glycol monomethyl ether acetate, or PGMEA) is an ester of acetic acid and 1-methoxy-2-propanol. Because it contains both an ester and an ether linkage, PGMEA has unique solvent properties and is valued as a solvent for oils, gums, and resins.

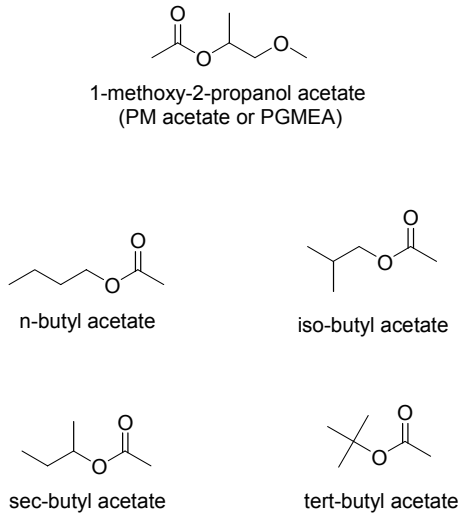

FIGURE 4.6 Structure of various esters.

Both butyl acetate and PGMEA are considered to have low toxicity in humans. Although hepatotoxicity has been seen in workers exposed to a mixture of solvents that included butyl acetate, no direct evidence supports butyl acetate as the agent responsible for the hepatotoxicity (Franco et al., 1986).

Only mild reproductive effects have been reported for butyl acetate in experimental animals. Increased testicular weights were reported in rats exposed to *n*-butyl acetate by inhalation over 13 weeks, but no testicular lesions accompanied the change in weight. *n*-Butyl acetate had no adverse effect on female fertility and fetal development (David et al., 2001). Another study found that pregnant rats exposed to *n*-butyl acetate had fetuses with lower weights than controls, but this was attributed to decreased food consumption by dams. No significant differences were seen in developmental defects in the fetuses of the exposure group, relative to controls, so the

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authors concluded that *n*-butyl acetate is not teratogenic (Elder, 1989). Unlike the ethylene glycol ethers, propylene glycol ethers and acetates, such as PGMEA, do not appear to have significant teratologic or reproductive toxicity effects. However, the PGMEA isomer 2-methoxy-1-propanol acetate, found as an impurity in commercial-grade PGMEA, has been reported to be teratogenic in both rats and rabbits. Because 2-methyoxy-1-propanol acetate can comprise as much as 5% of commercial PGMEA, the reproductive toxicity of this isomer may have implications for exposures to commercial-grade PGMEA.

KETONES

Ketones, organic compounds that contain a carbonyl functional group (C=O), are widely used as solvents and in chemical manufacturing (Rosenstock and Cullen, 1986). The general ketone structure is shown in Figure 4.7.

In general, ketones are not considered to be acutely toxic, and acetone, the most widely used ketone, is considered relatively nontoxic (Bruckner and Warren, 2001). As previously mentioned, some ketones produce a specific type of peripheral neuropathy that is mediated by their common metabolite, 2,5-hexanedione. There is no evidence that any of the ketones thought to have been sent to the Gulf War cause that peripheral neuropathy or have 2,5-hexanedione as a metabolite. There is evidence, however, that coexposure to some of the compounds sent to the Gulf War (specifically, methyl ethyl ketone and methyl isobutyl ketone) can potentiate peripheral neuropathies induced by *n*-hexane and methyl-*n*-butyl ketone (ATSDR, 1999; Ichihara et al., 1998). Although the exact mechanism of that potentiation is not clear, urinary concentrations of 2,5-hexanedione increased with potentiation of *n*-hexane neurotoxicity by methyl-*n*-butyl ketone (Ichihara et al., 1998).

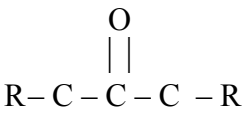

FIGURE 4.7 Basic structure of ketones.

PETROLEUM DISTILLATES

There was the potential for exposure to at least two refined-petroleum mixtures in the Gulf War: Stoddard solvent (dry-cleaning safety solvent) and naphtha. Stoddard solvent has many uses as a fuel or fuel additive, lubricant, dry-cleaning agent, chemical intermediate, and general cleaner and degreaser. Naphtha is used in paints, insecticide formulations, and solvent extraction processes and as a component in gasoline blending. Many fuels, including jet fuels, were used in the Gulf War. Those compounds are not reviewed in this volume of *Gulf War and Health*, however, because they will be reviewed in the next volume of *Gulf War and Health*.

Stoddard solvent is composed of a mixture of hydrocarbons (usually seven to 10 carbons long) that are produced during the refinement of crude oil. It is a colorless, flammable liquid that is insoluble in water. *Naphtha* is a general term for petroleum distillates that contain predominantly C_5–C_{13} aliphatic hydrocarbons.

The relative percentage of individual components affects the toxicokinetics of Stoddard solvent. A hydrocarbon's blood:air partition coefficient is a key factor in the rate

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and extent of its systemic absorption in the lungs. Aromatic compounds are absorbed more rapidly and completely through the lungs than are the long-chain aliphatic components, which have low solubility in the blood (Klaassen and Rozman, 1991). Nevertheless, the long-chain aliphatic components are also well absorbed. The internal doses of the individual components, therefore, will differ from their magnitudes of exposure.

Similarly, the toxicity of Stoddard solvent and naphtha is not usually determined by a single component, although the contribution of the individual hydrocarbons can influence the potential hazards associated with those compounds. 140°C Flash Stoddard solvent and naphtha contain the volatile hydrocarbons pentane through octane. This range of hydrocarbons includes hexane, a recognized neurotoxicant that causes a distal neurofilamentous axonopathy. *n*-Hexane's concentration in Stoddard solvent is low enough that it is not expected to pose a risk of induced peripheral neuropathy (Chang, 1987). No evidence of this type of injury has been identified in experimental animals after exposure to Stoddard solvent. Although one study in rats has shown decreased nerve conduction velocities in the tail axon, as well as axonal prenodal swelling and demyelinated foci after dermal exposure to white spirit formulations (Stoddard solvent is a type of white spirit) the swellings were mild and not of the neurofilamentous type (Verkkala et al., 1984). Other investigations have generally not corroborated those findings.

Hydrocarbon-induced renal toxicity has been observed in male rats after inhalation exposure. The renal toxicity is thought to arise from an $\alpha_{2\mu}$-globulin interaction, which results in the pathologic changes characteristic of the hydrocarbon-induced nephrotoxicity seen in male rats (Alden, 1986). Because $\alpha_{2\mu}$-globulin is peculiar to male rats, a similar renal toxicity is not expected to occur in humans. Renal toxicity has not been reported in humans, rabbits, guinea pigs, dogs, or monkeys.

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5

CANCER AND EXPOSURE TO INSECTICIDES

Unlike the following health outcome chapters that discuss health effects of insecticides and solvents in the same chapter, the cancer outcomes have been divided into two chapters. Chapter 5 focuses on the studies that examined cancer outcomes related to insecticide exposure, and Chapter 6 focuses on cancer outcomes related to solvent exposure. The issues encountered by the committee during its review of the relevant literature and the criteria it established in drawing conclusions about associations are discussed in the introduction of each chapter. Each chapter also presents a brief overview of the pertinent toxicologic information and findings from other organizations charged with evaluating the carcinogenicity of insecticides or solvents.

A general introduction to cancer and to cancer epidemiology that applies to both the insecticide and solvent literature is provided here. Furthermore, for each cancer type reviewed by the committee, an overview of the cancer, its risk factors, and 5-year survival rates, as identified by the National Cancer Institute (NCI) and the American Cancer Society (ACS), are presented in this chapter as background information.

The order of specific cancer sites reviewed by the committee in Chapters 5 and 6 is based on the ninth revision of the International Classification of Disease (ICD-9)[1] coding system.

CANCER OVERVIEW

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. Men in the United States have slightly less than a 50% lifetime risk of developing cancer, and women slightly more than a 33% lifetime risk (ACS, 2002a).

Cancer is characterized by the uncontrolled growth and spread of abnormal cells and can be caused by either external factors (chemicals, radiation, and viruses) or by internal factors (hormones, immune conditions, and inherited mutations) or both. Causal factors may act together or in sequence to initiate or promote the growth of abnormal cells. For adult

[1]ICD codes are revised and updated by the World Health Organization. Although ICD-10 codes have been published, ICD-9 codes remain the most widely recognized and used. ICD codes were established by the World Health Organization to promote international comparability in the collection, processing, classification, and presentation of mortality statistics. The codes group cancers according to their organ or tissue of origin and their histologic features.

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cancers, a latency period of 10 years or more may elapse between exposure and the detection of cancer (ACS, 2002a).

Lifestyle factors and environmental or occupational exposures—including smoking, diet, infectious diseases, and exposures to chemicals and radiation—are associated with an estimated three-fourths of all cancer deaths in the United States. On a population level, tobacco use, unhealthy diet, and physical inactivity are more likely to affect cancer risk than are trace amounts of pollutants in food, drinking water, and air. However, the degree of risk posed by pollutants depends on the dose and duration of exposure. For example, workers exposed to high concentrations of ionizing radiation, some chemicals, metals, and other substances have been shown to be at increased risk for cancer (ACS, 2002a).

Cancer Epidemiology and Insecticide Literature

Cancer is most likely the result of a multifactorial process over a lifetime, so it is difficult to establish definitive causal relationships. When investigating the factor or factors that may contribute to the development of cancer, epidemiologists must address several different issues, including environmental and occupational exposures, past lifetime activities (such as smoking), long latency periods, high fatality rates, and the need for accurate diagnoses; all of these issues are discussed in Chapter 2. Exposure determination, the role of confounding, and other broad epidemiologic issues considered by epidemiologists and the committee in evaluating the studies are also presented in Chapter 2. Issues germane to the cancer literature on exposure to insecticides and the decisions made by the committee in reviewing this literature are discussed below. Issues specific to the cancer literature and solvent exposure are discussed in the introduction of Chapter 6.

The pesticides identified by the US Congress, the Department of Defense, and the Department of Veterans Affairs as potentially being used during the Gulf War were all insecticides except for one insect repellent (*N,N*-diethyl-3-methylbenzamide [DEET]) (see Appendix D for complete list of insecticides reviewed by the committee). Therefore, the committee focused its review on exposure to insecticides in general, to classes of insecticides, and to specific insecticides. However, the literature on insecticides and cancer outcomes includes studies of occupations or populations—such as farmers, agricultural workers, and pesticide applicators—with exposure to numerous agricultural chemicals including insecticides. Most of those studies focus on exposure to pesticides as a broad group of chemical compounds. The term pesticide is often used in studies when the specific agents are not known or when a mixture of insecticides and other pest-control agents are thought to have been used. Use of pesticides could involve exposure to all types of pest-control agents—including insecticides, herbicides, fungicides, and other agents—and it is not possible to determine whether the reported associations with pesticide exposure are related to the specific insecticides of interest in this report. Most of the studies are occupational and use farmers, agricultural workers, or pesticide applicators as surrogates of exposure to the broad group of chemical agents known as pesticides. As a result, the potential for exposure misclassification bias is a limitation of those studies. The committee did not make conclusions of association on the broad category of pesticides because it includes herbicides, fungicides, and other agents not known to have been used during the Gulf War.

Another limitation of the literature is the small number of study subjects, which is due to the specificity of the exposure and the rarity of individual cancers. Although the

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studies on exposure to pesticides and cancer outcomes are limited by sample size and lack of exposure specificity, the committee reviewed these studies and provides a brief discussion of their strengths and limitations at the end of each cancer section. However, the studies on exposure to pesticides are not considered primary evidence for the committee's conclusions and are not included in the data analysis tables in the cancer sections.

It should be noted that for cancer sites on which no published studies of exposure to insecticides were available, the committee acknowledged the lack of data and did not draw a conclusion regarding association. Conclusions were drawn for all cancers in which a body of literature was available.

The committee focused its review of cancer outcomes on human studies that had comparison or control groups (cohort and case–control studies). Case reports, case series, review articles, and meta-analyses related to cancer were excluded from the committee's review. Studies that by design could not provide valid exposure assessment information or estimates of risk—such as ecologic, cross-sectional, proportionate mortality ratio (PMR), and mortality odds ratio studies—were reviewed by the committee but were not considered critical to its conclusions. The committee describes those studies in the relevant sections of Chapter 5 as supplementary evidence and identifies the limitations related to drawing conclusions about associations. However, the studies are not identified in the tables that accompany each cancer section, because they were not critical to the committee's conclusions. The specific limitations of ecologic, cross-sectional, PMR, and mortality odds ratio studies are described in Chapter 2.

Toxicity and Carcinogenicity

Toxicologic studies examine the direct effects of various agents on natural processes in organisms. They can determine whether a specific chemical is carcinogenic in animals (such as rodents or other animals). Some studies in rodents have demonstrated carcinogenic and tumorigenic effects following long-term or high-dose oral exposure to several insecticides under review in this report, although some have inconsistent results. For example, exposure to dichlorvos has led to leukemia, pancreatic adenoma, and squamous cell papilloma of the forestomach in certain experimental studies (ATSDR, 1997). The International Agency for Research on Cancer (IARC)[2], which is charged with evaluating and determining whether a chemical agent is carcinogenic in humans on the basis of evidence from studies on both humans and animals, has determined that dichlorvos is "possibly carcinogenic to humans." That classification is based on IARC's finding of "inadequate evidence" in humans and "sufficient evidence" in experimental animals of the carcinogenicity of dichlorvos (IARC, 1991).

With regard to malathion and lindane, hepatic cancers have been observed in studies on animals exposed to each (ATSDR, 1999, 2001a). IARC has reviewed hexachlorocyclohexanes, which include the gamma isomer known as lindane, and has determined that the insecticide is "possibly carcinogenic to humans" on the basis of "inadequate evidence" in humans and "limited evidence" in animals. IARC also found

[2] It is important to note the differences in the objective of the IARC program and the charge of this committee. The objective of the IARC program is to determine whether agents or occupational exposures are carcinogenic, whereas this committee is charged with determining whether or not there is an association between exposure to a specific agent or agents and a specific health outcome, such as a particular cancer.

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"sufficient evidence" of carcinogenicity of technical grade lindane and the alpha isomer in studies conducted on animals (IARC, 1987). The National Toxicology Program has concluded in its most recent report on carcinogens that lindane and hexachlorocyclohexanes are "reasonably anticipated to be human carcinogens" (NTP, 2001). IARC determined that exposure to malathion is not classifiable as to human carcinogenicity because the available animal studies did not provide evidence and no human studies were available to support a conclusion of carcinogenicity (IARC, 1983).

IARC has stated that exposure to carbaryl or permethrin insecticides are not classifiable as to human carcinogenicity, because of a lack of human studies and inadequate experimental evidence in animals (IARC, 1976, 1991). ATSDR has identified one pyrethroid, cypermethrin, as having produced lung tumors in animals (ATSDR, 2001b), but IARC has determined that permethrin, a related insecticide, is not classifiable as to human carcinogenicity, because animal studies yielded inadequate evidence and no human studies were available (IARC, 1991). No carcinogenic effects of long-term, high-dose exposure to the other insecticides reviewed in this report have been reported in the experimental literature.

The committee uses experimental evidence only in those instances as required by the definitions of the categories of association. Only the category of "Sufficient Evidence of a Causal Association" requires support from experimental evidence. For each conclusion of causality, animal and other experimental data are described that might provide a plausible mechanism for the outcome being discussed. None of the conclusions of association for exposure to insecticides and cancer outcomes are causal; however, a detailed discussion of the experimental evidence on the insecticides under review is provided in Chapter 3.

ORAL, NASAL, AND LARYNGEAL CANCERS

The cancers under review here are those of the lip (ICD-9 140.0–140.9), tongue (ICD-9 141.0–141.9), mouth (including the lining of the lips and cheeks) (ICD-9 144.0–145.9), pharynx (ICD-9 146.0–146.9), nasal or sinus cavity (ICD-9 160.0–160.9), nasopharynx (ICD-9 147.0–147.9), and larynx (ICD-9 161.0–161.9). Men are more likely than women to develop these cancers, and tobacco use, especially smoking, is a risk factor for both oral and laryngeal cancers. In addition to sex and smoking, other risk factors include alcohol consumption, vitamin A deficiency, exposure to ultraviolet radiation (sunlight), increasing age, a weakened immune system, and occupational exposure to glues and such other substances found in industry as petroleum, plastics, wood, textile, and leather working (ACS, 2000a, 2002b,c; NCI, 2002a,b).

Epidemiologic Studies of Exposure to Insecticides

The committee could not draw a conclusion regarding association between exposure to insecticides and oral, nasal, or laryngeal cancer, because of the lack of studies that examine exposure to insecticides and the risk of these cancers. Several studies evaluated the risk of those cancers among occupational groups—such as farmers, agricultural workers, and agricultural chemical workers (e.g., Blair et al., 1993; Franceschi et al., 1993; Reif et al., 1989; Sathiakumar et al., 1992; Wiklund and Steineck, 1988)—but none identified specific insecticide exposures.

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Until research with greater specificity of exposure is conducted, it is not possible to make a conclusion regarding association between exposure to insecticides and oral, nasal, or laryngeal cancers.

GASTROINTESTINAL TRACT CANCERS

Gastrointestinal tract tumors include some of the most common cancers in the United States: esophageal (ICD-9 150.0–150.9), stomach (ICD-9 151.0–151.9), colon (ICD-9 153.0–153.9), rectal (ICD-9 154.0–154.1), and pancreatic (ICD-9 157.0–157.9).

On the basis of data collected between 1992 and 1997, the 5-year relative survival rate for esophageal cancer is 14%. That rate has steadily increased over the last 20 years; in 1974–1976, it was 5% (ACS, 2002a). With nearly 3 times as many men affected as women, sex is a known risk factor for esophageal cancer. Furthermore, for unknown reasons, blacks are 2–3 times more likely to develop esophageal cancer than whites. The use of tobacco products and long-term heavy drinking are considered important risk factors. Other risk factors are advancing age; medical history of other head and neck cancers; long-standing gastric reflux or peptic ulcer of the esophagus (Barrett's syndrome); a diet lacking fruits, vegetables, and some minerals and vitamins; and pre-existing conditions, including achalasia of the cardia (failure of the lower esophageal sphincter to relax and allow food to pass) and esophageal webs (abnormal protrusions of tissue into the esophagus) (ACS, 2000b; NCI, 2002c).

The incidence of and mortality from stomach cancer in the United States have decreased over the last 60 years; the 5-year relative survival rate is 22% (ACS, 2002a). The disease is found most often in people over 50 years old and is more common in men and in blacks. Although the cause of stomach cancer is unknown, several studies have indicated that the presence of *Helicobacter pylori* bacteria, which can cause stomach inflammation and ulcers, may be a major risk factor. Other suggested risk factors are tobacco and alcohol abuse, stomach surgery, family history, stomach polyps, and diet, particularly diets high in smoked foods, high in salted fish and meat, and low in fiber (ACS, 2000c; NCI, 2002d).

Cancers of the colon and rectum, sometimes referred to together as colorectal cancer, are the third most common cancers in the United States, excluding skin cancers. The 5-year relative survival rate is 61% (ACS, 2002a). Colorectal cancer screening tests and improvements in nutrition and physical activity have decreased the development of these cancers (Frazier et al., 2000). Researchers have identified several risk factors, namely: family history of colorectal cancer or familial colorectal cancer syndromes; personal history of colorectal cancer, intestinal polyps, or chronic inflammatory bowel disease; physical inactivity; obesity; smoking; a diet high in animal fat; and age (most cases occur in people more than 50 years old) (ACS, 2001a; NCI, 2002e).

Although mortality from pancreatic cancer among men has declined somewhat over the last 20 years, men are still nearly 3 times more likely than women to develop this cancer. Risk increases with age; most cases occur in people 60–80 years old. Other potential risk factors are smoking, diabetes mellitus, chronic pancreatitis, family history, a diet high in animal fat, and occupational exposures, including those to some pesticides, dyes, and gasoline-related chemicals (ACS, 2000d; NCI, 2002f).

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Epidemiologic Studies of Exposure to Insecticides

A few studies investigated the risk of gastrointestinal tract tumors among farmers and agricultural workers, but no critical studies examined the risk associated with specific insecticides. Studies that have attempted to do so are limited by poor exposure determination, small numbers of exposed cases, lack of consideration of potential confounders, and possible recall bias in interview data. Results of the studies considered for evidence of association are presented in Table 5.1.

Stomach Cancer

No studies meeting the committee's criteria for critical studies were available that evaluated the risk of stomach cancer associated with exposure to the specific insecticides or classes of insecticides used in the Gulf War. One proportional cancer mortality study of Wisconsin farmers evaluated the risk of stomach cancer after insecticide exposure and reported an increased proportional cancer mortality ratio (Saftlas et al., 1987). However, as is explained in the introduction to this chapter, PMR studies were not considered primary evidence for the purpose of this evaluation because of the inherent limitations in that study design (see Chapter 2).

Colorectal Cancer

A cross-sectional study of serum concentrations of 19 organochlorines, including lindane, looked at exposure to specific insecticides and colorectal cancer (Soliman et al., 1997). However, of the insecticides examined in the study, only lindane is of interest for this report. The half-life of lindane in the body is short enough that a measure of contemporaneous exposure does not provide adequate evidence of exposure before the development of cancer, so this study did not consider a latency period between exposure and cancer outcome and therefore was not considered a critical study. In addition, the Wang and colleagues study (1988) of specific organochlorine exposure on a countywide level (using earwax) and colorectal cancer was not considered a critical study for drawing conclusions because exposure of individual subjects was not determined.

Rapiti and colleagues (1997) examined occupational risk factors for cancer mortality in a cohort of 505 men employed at any time from February 17, 1954, to August 31, 1970, in an Italian chemical production plant. Vital status was obtained through June 1991. A subject who had ever worked in insecticide production was considered exposed to insecticides. On the basis of one exposed case, the standard mortality ratio (SMR) was 0.75 (90% confidence interval [CI] = 0.04–3.54) for exposure to insecticides and colon and rectal cancer. The lack of verifiable individual exposure data and the fact that only one exposed case was identified severely limit the findings of this study, and the study was not considered to be critical to this review. Although the proportional cancer mortality study by Saftlas and colleagues (1987) mentioned above found an increased risk of rectal cancer associated with insecticide use in Wisconsin, it is not useful in supporting the body of evidence, as noted in the section above on stomach cancer.

Pancreatic Cancer

Alguacil and colleagues conducted a case–control study (2000) in five hospitals in eastern Spain to analyze the relationship between occupational exposure and pancreatic

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cancer. Histologically confirmed incident cases of pancreatic cancer (*n* = 185) and hospital-based controls (*n* = 264) were identified in 1992–1995. Trained personnel conducted interviews with cases and controls to assess lifetime history of disease, occupation, and lifestyle risk factors; industrial hygienists used this information to categorize exposure to 22 suspected carcinogens. A slight increase in pancreatic cancer risk (odds ratio [OR] = 1.27, 95% CI = 0.57–2.83) was observed in association with exposure to organophosphorous insecticides. The magnitude of risk varied with intensity and duration of exposure: OR = 1.8 (95% CI = 0.75–4.30) for cases exposed to high concentrations of organophosphorous insecticides for at least 6 months; OR = 1.2 (95% CI = 0.39–3.68) for those exposed to high concentrations of organophosphorous agents for at least 10 years, 10 years before diagnosis. However, all the findings related to pancreatic cancer and exposure to organophosphorous insecticides are weak, only a small number of cases were exposed, and the study is limited by the potential for selection bias due to the inclusion of controls with chronic (*n* = 93) or acute (*n* = 34) pancreatitis, other benign pathologic conditions (*n* = 70, mainly biliary), and other cancers (*n* = 41).

Ji and colleagues (2001) conducted a population-based case–control study on 484 pancreatic cancer cases diagnosed in 1986–1989 in Atlanta, Detroit, and New Jersey. Diagnosis was verified through review of medical charts, and both cases and 2095 population-based matched controls were interviewed to determine past occupations, history of disease, and lifestyle factors. A job–exposure matrix was used to classify each occupation's potential for and level of exposure to insecticides. No risk of pancreatic cancer was found to be associated with moderate to high exposure to insecticides (OR = 1.0, 95% CI = 0.4–2.5), on the basis of 10 exposed cases. Although this was a fairly large study, the use of occupational titles and categories of exposure as surrogates of exposure constitutes a limitation. Furthermore, because the job–exposure matrix was based exclusively on experience pertaining to the subject's usual occupation instead of the subject's total exposure, the potential for misclassification bias is another limitation that the committee considered in reviewing the evidence provided by the study.

Gastrointestinal Cancers

Many studies have investigated the relationship between pesticide exposure and the risk of cancers of the gastrointestinal tract. However, the term pesticides often includes exposure to different types of pest agents, such as insecticides, herbicides, fungicides, and other compounds that are not of specific interest in this review. Overall, the studies indicate a slight increase in gastrointestinal tumors among people exposed to pesticides, but most of the studies use industry type and job title, such as pesticide applicator, as surrogates of exposure. The lack of specificity of exposure of interest for this review and the potential for selection and recall bias are limitations of the studies, and the committee reviewed them as supplementary evidence in reaching its decision about associations. Some of the studies on exposure to pesticides and gastrointestinal cancers include: Alavanja et al., 1987, 1990; Cantor and Booze, 1991; Cocco et al., 1998a, 1999a; Fredriksson et al., 1989; Fryzek et al., 1997; Kauppinen et al., 1995; Paldy et al., 1988; Wesseling et al., 1999; Wiklund et al., 1989; and Zhong and Rafnsson, 1996.

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Summary and Conclusion

Overall, very few studies on exposure to insecticides and specific gastrointestinal tract tumors were available and met the criteria for this review. In fact, only studies on pancreatic cancer were of sufficient specificity and quality to make a conclusion regarding association. Most studies were limited by study design and the lack of specific and individual exposure information. As a result, the committee did not draw a conclusion regarding association for esophageal cancer, stomach cancer, or colorectal cancer, because of the lack of pertinent studies of exposure to the insecticides under review. Based on the studies identified in Table 5.1, the committee was able to make a conclusion of inadequate/insufficient between exposure to insecticides and risk of pancreatic cancer.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and pancreatic cancer.

TABLE 5.1 Selected Epidemiologic Studies—Pancreatic Cancer and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Class of Insecticides—Organophosphorous agents			
Case–Control Study			
Alguacil et al., 2000	Residents of Spain		
	All exposed patients	17	1.27 (0.57–2.83)
	Highly exposed (6+ months)	16	1.80 (0.75–4.30)
	Highly exposed (10+ years, 10 years before diagnosis)	9	1.20 (0.39–3.68)
Insecticides			
Case–Control Study			
Ji et al., 2001	Residents of United States		
	Low exposure	45	0.5 (0.3–0.9)
	Moderate/high exposure	10	1.0 (0.4–2.5)

HEPATOBILIARY CANCERS

Hepatobiliary cancers comprise cancers of the liver, bile duct, gallbladder, and biliary tract (ICD-9 155.0–156.9). The overall 5-year survival rate for liver cancer is relatively low at 6% (ACS, 2002a). More cases of gallbladder and other biliary tract cancers occur in men than in women. Other reported risk factors related to hepatobiliary cancers are chronic infection with the hepatitis B virus (alone and in combination with aflatoxin) or hepatitis C virus and cirrhosis of the liver. Cirrhosis is usually due to excessive alcohol consumption but can also be caused by hepatitis B, hepatitis C, or hemochromatosis, a hereditary disease in which too much iron is absorbed from food. Exposure to aflatoxin, vinyl chloride, thorium dioxide, or arsenic in drinking water and long-term anabolic steroid use have also been linked to hepatobiliary cancers (ACS, 2001b; NCI, 2002g).

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Epidemiologic Studies of Exposure to Insecticides

No well-conducted studies have examined the risk of hepatobiliary cancers in relation to specific insecticide exposure. The studies that are available on classes of insecticides or unspecified insecticides are few, lack consistency of effect, and often do not adequately control for confounding (from alcohol consumption or hepatitis B or C infection). Most studies examine the risk of liver cancer broadly; those that identify more specific cancers are identified below. The key studies reviewed by the committee are discussed below and results are in Table 5.2.

No studies involving specific insecticides were considered critical for review by the committee. An ecologic study by Wang and colleagues (1988) conducted in China correlated concentrations of organochlorines (including lindane) in earwax in a sample of adults in a county with county liver cancer mortality data. As discussed in the introduction to this chapter, the committee determined that ecologic study design is of little value in drawing conclusions of association due to its limitations.

A case–control study conducted by Cordier and colleagues (1993) examined the effects of organophosphorous insecticides and other pesticides on the risk of hepatocellular carcinoma (HCC). The investigators identified 152 HCC cases in two hospitals in northern Vietnam diagnosed in 1989–1992. Hospital controls (n = 241) were frequency matched on the basis of sex, age, hospital, and residence. Patients with a history of cancer were excluded from both the case and control groups. Self-reported agricultural use of organophosphorous insecticides (at least 30 L/year) was strongly associated with risk of HCC (OR = 4.7, 95% CI = 1.1–20.1); there were 13 exposed cases. However, the risk did not increase with increased insecticide use; no positive associations were observed with use below 30 L/year. A strength of this study is that the authors adjusted for hepatitis B status and alcohol consumption (two known risk factors for HCC and potential confounders) with unconditional logistic regression. However, it is limited by the self-reporting of exposure (which is subject to recall bias), the use of other pesticides, and the small number of exposed cases. In particular, the lack of an exposure–response relationship suggests that the reported exposure to organophosphorous agents could have been confounded by other exposures possibly associated with liver cancer. Cases included in the study were only a subset of all HCC cases, and histologic information was not available on most of the cases included. Bias may also have occurred because of the high proportion of controls with gastroduodenal ulcers, which have been related to higher tobacco consumption and lower alcohol use.

Forty-four liver and biliary tract cancer cases were identified from 6259 death certificates among a cohort of 21,437 male Dow chemical-plant workers in Michigan in 1940–1982 (Bond et al., 1990). A control group of 1888 nonexposed workers was chosen randomly from the original cohort of hourly employees. Exposure to insecticides was determined from company work-history records; workers with either a major or a minor work assignment in the insecticide manufacturing unit were considered exposed. No association was observed between work in insecticide production areas and risk of liver or biliary tract cancer (OR = 0.6, 95% CI = 0.1–2.4) on the basis of two cases. Work area was used as a surrogate of exposure, and the number of exposed cases was small, limiting the interpretation of the findings of this study.

The study of Italian chemical production plant workers described previously reported an SMR of 2.04 (90% CI = 0.36–6.42) for work in the insecticide production process and

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liver cancer (Rapiti et al., 1997). The lack of verifiable individual exposure data and the fact that only two cases were exposed are limitations of this study.

Several studies examined the relationship between exposure to the broader category pesticides (which includes insecticides, fungicides, herbicides, and other pest agents) and hepatobiliary cancers among various occupationally exposed populations. Although several studies demonstrated an increase of hepatobiliary cancers among pesticide applicators and manufacturers (e.g., Amoateng-Adjepong et al., 1995; Figa-Talamanca et al., 1993a,b; Fleming et al., 1999a,b; Pesatori et al., 1994; Thomas et al., 1996), the use of job titles as surrogates of exposure does not provide specific or validated exposure information at the individual level. Furthermore, depending on the nature of the work, the various occupational groups are exposed to a multitude of chemicals other than insecticides, including organic dusts, solvents, other agricultural chemicals, fuels and engine exhausts, and infectious microorganisms; such exposure limits the value of these findings in supporting an association between exposure to insecticides and hepatobiliary cancers.

Summary and Conclusion

No studies reviewed examined specific insecticide use and the risk of hepatobiliary cancers. The studies that do contain relevant exposure data provide inconsistent measures of association across exposure classifications, no increasing risk with increasing exposure, and small numbers of exposed cases. Table 5.2 identifies the literature with relevant findings.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and hepatobiliary cancers.

TABLE 5.2 Selected Epidemiologic Studies—Hepatobiliary Cancers and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Class of Insecticide— Organophosphorous agents			
Case–Control Study			
Cordier et al., 1993	Residents of northern Vietnam		
	1–9 L/year	19	1.1 (0.4–2.9)
	10–19 L/year	4	0.7 (0.1–3.9)
	20–29 L/year	3	0.4 (0.1–2.5)
	≥30 L/year	13	4.7 (1.1–20.1)
Insecticides			
Cohort Study			
Rapiti et al., 1997	Male workers at Italian chemical production plant	2	2.04 (0.36–6.42)[a]
Case–Control Study			
Bond et al., 1990	Male chemical workers in Michigan	2	0.6 (0.1–2.4)

[a]90% CI

LUNG CANCER

Lung cancer (carcinoma of the lung and bronchus, ICD-9 162.2–162.9) is the leading cause of cancer death among both men and women in the United States, and smoking is the

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strongest risk factor. Other environmental risk factors for lung cancer are exposure to asbestos, radon gas, second-hand tobacco smoke, such radioactive ores as uranium, and chemicals, including arsenic, vinyl chloride, coal products, and mustard gas. People with tuberculosis, some types of pneumonia, silicosis, or berylliosis may also be at increased risk for lung cancer (ACS, 2002d; NCI, 2002h). Although great strides have been made in treating lung cancer, the 5-year relative survival rate is only 15% (ACS, 2002a).

Epidemiologic Studies of Exposure to Insecticides

As with several of the other cancer sites, very few studies examine the risk of lung cancer in relation to specific insecticides. Studies that do provide some specificity—whether examining exposure to a specific compound, a class, or the general category of insecticides—are few and do not show a consistent effect. The studies reviewed also did not specify the type of respiratory cancer but focused broadly on lung cancer. The key studies reviewed by the committee are discussed below, including their strengths and limitations. The results are provided in Table 5.3. The committee assessed whether each study adequately controlled for smoking, a major risk factor for lung cancer and an important potential confounder (see Chapter 2 and Appendix E).

Pesatori and colleagues (1994) conducted a nested case–control study of 65 deceased pest-control workers with lung cancer recorded on death certificates as an underlying or contributing cause of death and pest-control worker controls (122 deceased and 172 living) selected from a cohort of Florida pest-control workers whose companies applied for licenses to the Florida Department of Health and Rehabilitative Services in 1965–1966. Exposure to specific insecticides was determined from interviews with next of kin for all subjects, including the living controls. Higher risks of lung cancer than in living controls were reported in association with exposure to diazinon, carbaryl, and propoxur; no association was seen with exposure to malathion or chlorpyrifos, as shown in Table 5.3. Almost all the associations were weak, and the CIs were generally wide, probably because of the small numbers of exposed cases. The ORs using dead controls were consistently somewhat higher than when living controls were used in the analysis; given that all interviews were with proxies, this is difficult to explain. The study was limited by the use of proxy interviews to determine exposure, which could introduce a number of biases.

Using the Saskatchewan Cancer Foundation registry, McDuffie and colleagues (1990) identified 273 primary lung cancer cases diagnosed in 1983–1986. Population-based control subjects (n = 187) were identified from records of the Saskatchewan Hospital Services Plan. All participants were interviewed to determine occupational exposure, medical history, and smoking status. The smoking-adjusted OR for lung cancer and exposure to carbamates was less than 1.0 and suggested no risk of lung cancer from exposure. Analysis of the 451 cases who were initially contacted but declined to be interviewed revealed a tendency for younger cases to be more likely to participate than older cases, which led to a potential for selection bias.

Pesatori and colleagues (1994) also evaluated exposure to insecticides grouped by class in the study of pest-control workers described above. Risk of lung cancer was increased for organophosphorous insecticides (OR = 2.0, 95% CI = 0.8–5.0) and carbamates (OR = 1.8, 95% CI = 0.5–6.4) as reported by next of kin, but results showed considerable uncertainty. Limitations of the study, as noted above, apply to these results as well.

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The cohort study of 505 male workers at an Italian chemical production plant described earlier in the gastrointestinal cancer section found an SMR of 0.80 (90% CI = 0.27–1.82) for exposure to insecticides and lung cancer on the basis of four exposed cases (Rapiti et al., 1997). The lack of verifiable and specific individual exposure data and the small number of exposed cases limit the value of the findings of this study. No additional associations were found between lung cancer and insecticides in the case–control study in Saskatchewan described above (McDuffie et al., 1990).

Several studies examined the relationship between pesticides and lung cancer among various occupationally exposed populations. As mentioned previously, the committee reviewed this literature as supplementary evidence in drawing its conclusion about associations. Studies of pesticide applicators and agricultural workers (e.g., Amoateng-Adjepong et al., 1995; Figa-Talamanca et al., 1993a,b; Fleming et al., 1999a,b; Pesatori et al., 1994; Thomas et al., 1996) provide inconsistent measures of effect and often use job titles as surrogates of exposure. The lack of exposure specificity limits the findings of these studies in determining an association between exposure to insecticides used in the Gulf War and lung cancer risk.

Summary and Conclusion

A number of epidemiologic studies have examined the relationship between lung cancer and exposure to the broad group of pesticides, but few examine the association with specific insecticides. One study (Pesatori et al., 1994) reported positive associations between some specific insecticides and lung cancer but the associations were not strong, were based on small numbers of exposed cases, and were not consistent with respect to analyses of living versus deceased controls. Other studies that contain relevant exposure estimates yield inconsistent associations (such as with carbamates) or negative associations (such as with insecticides in general). Table 5.3 identifies the body of literature reviewed and the relevant findings.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and lung cancer.

TABLE 5.3 Selected Epidemiologic Studies—Lung Cancer and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific Insecticides			
Cohort Study			
Pesatori et al., 1994	Pest-control workers in Florida		
	Living controls [a]		
	Diazinon	17	1.3 (0.6–3.1)
	Malathion	11	1.0 (0.4–2.6)
	Chlorpyrifos	3	0.6 (0.1–2.4)
	Carbaryl	3	4.2 (0.6–27.2)
	Propoxur	5	1.4 (0.4–5.5)
	Deceased controls [a]		
	Diazinon	17	2.0 (0.7–5.5)
	Malathion	11	1.6 (0.5–4.6)
	Chlorpyrifos	3	1.3 (0.2–7.1)
	Carbaryl	3	NA
	Propoxur	5	12.4 (1.5–100.3)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Classes of Insecticide			
Cohort Study			
Pesatori et al., 1994	Pest-control workers in Florida		
	Living controls[a]		
	Organophosphorous agents	23	2.0 (0.8–5.0)
	Carbamates	7	1.8 (0.5–6.4)
	Deceased controls[a]		
	Organophosphorous agents	23	2.2 (0.8–5.8)
	Carbamates	7	16.3 (2.2–122.5)
Case–Control Study			
McDuffie et al., 1990	Male cases from Saskatchewan Cancer Foundation Registry		
	Carbamates	9	0.46[a]
Insecticides			
Cohort Study			
Rapiti et al., 1997	Male workers at Italian chemical production plant	4	0.80 (0.27–1.82)[b]
Case–Control Study			
McDuffie et al., 1990	Male cases from Saskatchewan Cancer Foundation registry		
	Other insecticides[c]	19	0.95[a]

[a]Results are adjusted for smoking.
[b]90% CI.
[c]Insecticides other than chlorinated hydrocarbons, arsenic, carbamates, or phosphodithioate

BONE CANCER

Of the several forms of primary bone and joint cancer (ICD-9 170.0–170.9), osteosarcoma is the most common primary bone cancer, accounting for about 35% of all cases. Occurring more frequently in males, osteosarcoma is found mostly in people 10–30 years old and rarely during middle age. About 10% of cases develop in people 60 years old and older. Other, rare forms of primary bone cancer include chondrosarcoma (cancer of cartilage cells), Ewing's tumor (cancer of the bone cavity), chordoma (cancer of the skull base and spinal bones), and malignant fibrous histiocytoma and fibrosarcoma (cancer of the connective tissues). The 5-year survival rate can be as high as 80%, but the prognosis for people with primary bone cancer varies greatly, depending on the specific type of cancer and the stage at which it is diagnosed (ACS, 2000e; NCI, 2002i).

Risk factors for bone cancer are exposure to ionizing radiation, particularly at an early age or at high doses; a history of bone disorders, such as Paget's disease; and the presence of multiple exostoses (overgrowths of bone tissue), multiple osteochondromas (benign bone tumors formed by bone and cartilage), multiple enchondromas (benign cartilage tumors), and some genetic factors (such as mutation of the p53 tumor-suppressor gene) (ACS, 2000e; NCI, 2002i).

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Epidemiologic Studies of Exposure to Insecticides

Several studies have examined the risk of bone cancer among farmers and agricultural workers (e.g., Blair et al., 1993; Brownson et al., 1989; Reif et al., 1989), but no studies provided an analysis of exposure to the specific insecticides under review or insecticides in general and bone cancer.

An evaluation of any association between insecticides and bone cancer cannot be made until research with greater specificity of exposure is conducted.

SOFT TISSUE SARCOMA

An uncommon form of cancer, soft tissue sarcoma (STS) (ICD-9 171.0–171.9, 164.1) makes up less than 1% of incident cancer cases each year, and the 5-year survival rate is about 90% (ACS, 2002e). About 10% of cases occur in children and adolescents under 20 years old (NCI, 2002j).

There have been only a few studies of risk factors for STS, so the risk factors are not well understood. However, people with alterations in the p53 gene (Li-Fraumeni syndrome) or the NF1 gene (neurofibromatosis, or von Recklinghausen disease) and people with family histories of Gardner's syndrome (colonic polyps) or retinoblastoma are at increased risk for STS. External ionizing radiation is suspected to cause a small percentage of sarcomas (less than 5%), and exposure to some chemicals—such as vinyl chloride, dioxin, and phenoxyacetic acid—may also play a role (ACS, 2002e). Chemotherapeutic agents that cause secondary sarcomas in cancer survivors are also being investigated (Zahm, 1997).

Epidemiologic Studies of Exposure to Insecticides

This section reviews the available literature on exposure to insecticides and STS. The following discussion highlights the key studies reviewed in drawing a conclusion and Table 5.4 provides results from these studies.

Only one study, an ecologic study, investigated exposure to a specific insecticide, diazinon, and the risk of STS (Mills, 1998). Although a specific insecticide is identified, the study is limited by the fact that mortality is correlated with the number of pounds of insecticide used in the state, which means that exposure and outcome are not on an individual level. Exposure and outcome were also contemporaneous, so no latency period existed between time of exposure and diagnosis of cancer. Thus, as is indicated at the beginning of the chapter, the study was not considered to be useful for the purpose of this review because of its study design limitations.

One population-based case–control study examined the effect of agricultural exposures and the risk of STS (Zahm et al., 1988). Cases were selected from among white men 21 years old or older living in Kansas in 1976–1982. A total of 133 STS cases of the 139 eligible after pathologic review were interviewed by telephone. Population-based controls were matched 3:1 on age and vital status. On the basis of self-reported exposure information, an increase in STS risk was associated with ever using organophosphorous insecticides on animals (OR = 2.1, 95% CI = 0.6–6.9), insecticides in general (OR = 1.3, 95% CI = 0.8–2.2), and insecticides on animals (OR = 1.6, 95% CI = 0.9–2.5). However, no increased risk of STS was observed in those using insecticides on crops (OR = 0.8, 95% CI

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= 0.4–1.6). Farmers were also asked about prior use of carbamates, but no cases reported exposure to this class of insecticide. Use of crop insecticides resulted in no association with STS (OR = 0.8, 95% CI = 0.4–1.6). The study, however, is limited by the potential for exposure misclassification because exposure levels were based on insecticides in general and the classes organophosphorous insecticides and carbamates.

Several studies examine the relationship between exposure to pesticides in general and STS risk. As indicated in the introduction of this chapter, although studies of pesticides were reviewed, they yielded secondary support for conclusions. Some of the studies on pesticide exposure and STS risk include: Fleming et al., 1999a,b; Franceschi and Serraino, 1992; Kristensen et al., 1996; Wiklund et al., 1989; and Zahm et al., 1988.

Summary and Conclusion

Overall, the value of the body of evidence on exposure to insecticides and the risk of STS was limited by the lack of studies. In the one case–control study providing evidence for conclusions, there was not a clear relationship between classes of insecticides known to be present in the Gulf War and STS.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and soft tissue sarcomas.

TABLE 5.4 Selected Epidemiologic Studies—Soft Tissue Sarcomas and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Class of Insecticides and Insecticides			
Case–Control Study			
Zahm et al., 1988	Residents of Kansas		
	Organophosphorous agents	5	2.1 (0.6–6.9)
	Animal insecticides	46	1.6 (0.9–2.5)
	Crop insecticides	14	0.8 (0.4–1.6)
	Insecticides	50	1.3 (0.8–2.2)

SKIN CANCER

Cancers of the skin are divided into two general types: melanoma and nonmelanoma skin cancers. Together, they are the most common form of cancer in the United States, accounting for more than 40% of all cancers diagnosed each year (ACS, 2001c).

Nonmelanoma skin cancers (ICD-9 173.0–173.9) are the most prevalent form of skin cancer. They are highly curable, with a 5-year survival rate of 95–99% (ACS, 2001c). Risk factors associated with the development of nonmelanoma skin cancer include excessive exposure to ultraviolet radiation (particularly from sunlight but also from tanning lamps and booths); fair complexion; chemical exposure to such substances as arsenic, industrial tar, coal, and some oils; and exposure to ionizing radiation, usually during the course of medical treatment. Sex is also an important risk factor: men are twice as likely as women to develop

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basal cell cancers and 3 times as likely to develop squamous cell carcinomas (ACS, 2001c; NCI, 2002k).

The most serious form of skin cancer is melanoma (ICD-9 172.0–172.9), which accounts for only 4% of all skin cancers, but nearly 79% of all skin cancer deaths. If it is diagnosed early, the 5-year relative survival rate is more than 90% (ACS, 2001d, 2002a; NCI, 2002l). The risk of developing melanoma increases with age, but it is one of the most common cancers in people under 30 years old. Other risk factors include excessive exposure to ultraviolet radiation, sunburn, fair complexion, family history of melanoma, immune suppression, and the presence of dysplastic or congenital melanocytic nevi (moles) (ACS, 2001d; NCI, 2002l).

Epidemiologic Studies of Exposure to Insecticides

No epidemiologic studies were identified in the committee's literature review on the relationship between exposure to specific insecticides and skin cancer, and only one study on insecticides in general was identified. The insecticide study reviewed by the committee is discussed below and Table 5.5 provides the results.

The only study on exposure to insecticides and skin cancer reviewed was a case–control study of 226 male basal cell carcinoma cases and 180 male squamous cell carcinoma cases conducted in Alberta, Canada, in 1983–1984 (Gallagher et al., 1996). Controls (n = 406) were randomly selected from insurance subscriber files and frequency matched on 5-year age groups. Trained personnel interviewed all participants to determine skin, hair, and eye pigmentation; medical history; and past occupational exposures, including exposures to insecticides. Interviewers were blinded to the study hypothesis and the disease status of each participant. An increased risk of basal cell carcinoma (OR = 1.3, 95% CI = 0.9–2.1) and squamous cell carcinoma (OR = 1.7, 95% CI = 1.1–2.7) was associated with self-reported exposure to insecticides. Insecticide use was further stratified by high and low exposure in relation to squamous cell carcinoma risk. An increased risk (OR = 2.8, 95% CI = 1.4–5.6) was found for squamous cell carcinoma and high exposure to insecticides. Odds ratios were adjusted for age, skin color, hair color, mother's ethnic origin, and occupational sunlight exposure but not for recreational sunlight exposure, herbicides, fungicides, or other occupational exposures. The study's findings, however, are subject to recall bias, and other studies on exposure to insecticides and nonmelanoma skin cancers would be needed to substantiate an association.

Several studies examined the relationship between exposure to pesticides in general and risk of skin cancer; some of those studies are: Corrao et al., 1989; Fleming et al., 1999b; Holly et al., 1996; Morgan et al., 1980; Torchio et al., 1994; Wang and MacMahon, 1979; and Wesseling et al., 1999.

Summary and Conclusion

Given that only one study was available that examines exposure to insecticides in general and skin cancer, there is not sufficient evidence for drawing a conclusion regarding association for skin cancer risk. Additional studies on the exposure to insecticides under review in this report and the risk of skin cancer are needed before a conclusion can be drawn.

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TABLE 5.5 Selected Epidemiologic Studies—Skin Cancers and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Insecticides			
Case–Control Study			
Gallagher et al., 1996	Residents of Alberta, Canada		
	Basal cell carcinoma	50	1.3 (0.9–2.1)
	Squamous cell carcinoma	57	1.7 (1.1–2.7)
	Low insecticide exposure	21	0.7 (0.3–1.4)
	High insecticide exposure	36	2.8 (1.4–5.6)
			p trend = 0.02

FEMALE REPRODUCTIVE CANCERS

Female reproductive cancers include cancers of the breast, cervix, uterus, and ovaries. Breast cancer (ICD-9 174.0–174.9 for females) is the most common form of cancer among women and the second most common cause of death from cancer in women, exceeded only by lung cancer (ACS, 2001e). ACS estimates that nearly one in eight women in the United States will have breast cancer. If the tumor is diagnosed while still localized, however, the 5-year survival rate is 96% (ACS, 2002a).

Although considerable efforts have been made, little is known about the etiology of breast cancer. Risk factors generally include family history, mutations in the BRCA1 or BRCA2 (tumor-suppressor) genes, atypical breast hyperplasia, early menarche, late menopause, late childbearing or nulliparity, high breast density, exposure to ionizing radiation, hormone use, obesity, and alcohol use (ACS, 2001e; NCI, 2002m). However, many women who develop breast cancer do not have any of those risk factors.

Most cancers of the cervix (ICD-9 180.0-180.9) are squamous cell carcinomas, and the 5-year survival rate is about 70%. Women are at greater risk for cervical cancer if they or their partners began having sexual intercourse before the age of 18 years or if they have had many sexual partners. That is because of the correlation of cervical cancer and human papilloma viruses, which are believed to initiate abnormal cervical growth (NCI, 2002n).

About one in 57 US women will develop ovarian cancer (ICD-9 183.0) (NCI, 2002o). In contrast with the high 5-year survival rates for other female reproductive cancers, the survival rate for ovarian cancer is 52%. However, if diagnosed early and treated while localized, the 5-year survival rate is 95%. Because of its vague signs and symptoms (such as enlargement of the abdomen and digestive disturbances), ovarian cancer is not always detected early (ACS, 2002a). Risk factors for ovarian cancer include family history, age, childbirth, and the use of fertility drugs, hormone replacement therapy, or talc powder in the genital region (ACS, 2002a).

The 5-year survival rate for cancer of the uterus (ICD-9 179.0-182.8) is a relatively high at 84%. The incidence is higher among white women than among black women, but the case-fatality rate is reversed with black women having nearly twice as high fatality as white women. A major risk factor for uterine cancer is high cumulative exposure to estrogen. Use of estrogen-replacement therapy or tamoxifen, early menarche, late menopause, never having children, and lack of ovulation over long times are risk factors associated with the development of cancer of the corpus, or body, of the uterus. In contrast, pregnancy and the

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use of oral contraceptives appear to provide some protection against endometrial cancer, or cancer of the lining of the uterus (ACS, 2002a; NCI, 2002p).

Epidemiologic Studies of Exposure to Insecticides

A number of epidemiologic studies have investigated breast cancer risk and exposure to pesticides, with particular attention to the role of specific organochlorine pesticides, including dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), oxychlordane, mirex, hexachlorobenzene, and lindane. However, unlike other classes of insecticides (such as organophosphorous insecticides and carbamates), which share mechanisms and metabolic properties, lindane differs substantially from other organochlorine insecticides in its toxicity, absorption, metabolism, and other characteristics (see Chapter 3). The committee therefore focused its review on lindane and its isomers specifically and not on the larger class of organochlorines (see Chapter 2). Table 5.6 provides the key data points from the critical studies that the committee evaluated in making its conclusions.

Some studies have investigated the relationship between household and occupational exposures to pesticides and female reproductive cancers other than cancer of the breast, but no studies focused specifically on exposure to insecticides. Studies that do examine the risk of cervical, ovarian, or uterine cancer lack specific exposure information on insecticides and often involve extremely small numbers of cases (e.g., Fleming et al., 1999a,b; Wesseling et al., 1999).

Results of three nested case–control studies of serum concentrations of organochlorines, including lindane and its isomers, that were collected before breast cancer diagnosis, and breast cancer risk were primarily negative. Ward and colleagues (2000) conducted a nested case–control study in Norway of breast cancer risk and serum organochlorines in a cohort of 25,431 female serum bank donors in 1973–1991. They measured 71 organochlorine compounds, including γ-1,2,3,4,5,6-hexachlorocyclohexane (HCH), otherwise known as lindane. The study found no evidence of higher serum concentrations of any of these compounds in cases or any trend of increasing risk associated with higher quartiles of exposure to lindane (OR = 0.7, 95% CI = 0.1–4.0).

Another nested case–control study evaluated the association between serum organochlorine insecticides—including lindane and β-HCH (an isomer of HCH)—and breast cancer risk by using the Columbia, Missouri Breast Cancer Serum Bank, where samples for 7224 women diagnosed with breast cancer in 1977–1987 had been stored (Dorgan et al., 1999). The study found no increased risk of breast cancer in women with higher serum organochlorine insecticides (OR = 0.6, 95% CI = 0.3–1.3 for β-HCH).

In a third nested case–control study, Hoyer and colleagues (1998) compared serum concentrations of 18 organochlorine pesticides in baseline blood samples from 240 breast cancer cases and 477 controls selected from participants in the Copenhagen City Heart Study. They found no association with lindane or other organochlorines, such as DDT, DDE, and polychlorinated biphenyls; however, breast cancer risk was increased with higher β-HCH levels (OR = 1.36, 95% CI = 0.79–2.33).

Zheng and colleagues (1999) directly compared benzene hexachloride (BHC) in breast adipose tissue from 304 incident breast cancer cases and 186 benign breast disease cases as controls, and found no association between BHC isomers (including lindane) and

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risk of breast cancer. An inverse association with breast cancer risk was observed among all study subjects ($OR_{\beta\text{-BHC}} = 0.6$, 95% CI = 0.3–1.1) and among premenopausal and postmenopausal women when the highest quartiles of adipose tissue BHC were compared with the lowest.

Other hospital-based case–control studies of breast cancer risk and organochlorines, including lindane and its isomers, in breast tissue have reported inconsistent results (Dewailly et al., 1994; Falck et al., 1992; Guttes et al., 1998; Mussalo-Rauhamaa et al., 1990). Measurement of the compound in tissue does not allow for a latency period or exposure in the past. Another important issue that must be considered when evaluating studies on lindane or related isomers in breast fat tissue is the degree of control for confounding by other risk factors, such as parity and dietary fat.

A number of studies have focused on subjects considered to have been exposed to an undefined mixture of pesticides on the basis of their occupations or job titles, such as farmers or agricultural workers. However, those studies do not provide the specific information on exposure to insecticides needed for this review. Such studies of pesticides and breast cancer include those by Fleming and colleagues (1999a,b) and Cocco and colleagues (1998b).

Summary and Conclusion

In summary, the studies reviewed do not support an association between environmental exposure to lindane or any of its isomers and breast cancer risk. Caution must be exercised in interpreting the results of the studies because they have several limitations, including very small numbers of participants and the fact that tissue samples in hospital-based studies were collected after diagnosis of the disease. It is unknown whether concentrations of the compounds in question reflect exposures at the time of disease onset or whether the disease process itself or treatment affected the body burden of the compounds. Internal measures of dose are generally considered superior to external measures or job titles used as crude surrogates of exposure. A favorable feature of the nested case–control studies was the prospective design. The studies reviewed by the committee and the relevant data points are identified in Table 5.6. No studies examined exposure to specific insecticides, classes, or insecticides in general and cancer of the cervix, ovary, or uterus; therefore, the committee cannot draw a conclusion regarding association between exposure to insecticides and these female reproductive cancers.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to lindane or its isomers and breast cancer.

TABLE 5.6 Selected Epidemiologic Studies—Breast Cancer and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Lindane and Related Isomers			
Cohort Studies			
Ward et al., 2000	Female serum bank donors in Norway		
	γ-HCH	7	0.7 (0.1–4.0)[a]
	β-HCH, highest quartile of lipid-adjusted data	144	0.7

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Dorgan et al., 1999	Female serum bank donors in Columbia, Missouri Highest quartile of serum β-HCH	27	0.6 (0.3–1.3)
Hoyer et al., 1998	Female serum samples from Copenhagen City Heart Study Highest quartile of serum β-HCH	63	1.36 (0.79–2.33)[b]
Case–Control Studies			
Zheng et al., 1999	Breast adipose tissue from women in Connecticut Highest quartile of serum β-BHC	77	0.6 (0.3-1.1)
Mussalo-Rauhamaa et al., 1990	Breast tissue from women in Helsinki β-HCH	24	10.51 (2.00–55.26)[c]

[a]OR calculated from discordant pairs.
[b]Adjusted analysis.
[c]Controlled for age and parity.

UROLOGIC CANCERS

Cancers of the genitals or urinary tract include tumors of the prostate, testes, bladder, kidneys, and urinary tract. Urologic cancers account for about 41% of all cancers in men and 4% in women (ACS, 2002a).

Prostate cancer (ICD-9 185) accounts for nearly 30% of all male cancers, making it the most common cancer, excluding skin cancers, in American men (ACS, 2002a). The greatest risk factor is age; most cases occur in men over 65 years old. Other factors include family history of prostate cancer, race (prostate cancer occurs almost 70% more often in black men than in whites), and a high-fat diet (NCI, 2002q).

Although accounting for only about 1% of all cancers in men, testicular cancer (ICD-9 186.0–186.9) is the most common form of cancer in men 15–35 years old. It is one of the most curable types of cancer, with an average 5-year survival rate of more than 90%. In addition to age, risk factors are race (testicular cancer is more common in white men than in black or Asian American men), an undescended testis (cryptorchidism), abnormal testis development, Klinefelter syndrome (XXY chromosomal makeup), and family history of testicular cancer (ACS, 2000f; NCI, 2002r).

Bladder cancer (ICD-9 188.0–188.9) is the sixth most common form of cancer in the United States, excluding nonmelanoma skin cancers (ACS, 2002a). Smoking is considered the most widespread and modifiable risk factor for bladder cancer; smokers are about twice as likely as nonsmokers to develop the disease. Other risk factors include race (whites are twice as likely as blacks to be affected), sex (men are 3 times more likely to be affected than women), increasing age, and history of chronic bladder inflammation (ACS, 2001f; NCI, 2002s). Occupational exposure to carcinogens—such as benzidine and beta-naphthylamine, as seen among dye and rubber industry workers—has also been associated with significantly increased risks of bladder cancer (Miyakawa et al., 2001). Other occupations considered to pose a risk include working in the leather, textile, paint, and printing industries (ACS, 2001f).

Kidney cancer (ICD-9 189.0–189.9) shares some of the risk factors of bladder cancer, including smoking and occupational exposures, such as to asbestos, cadmium, dyes, and some organic solvents. Increased weight has been associated with kidney cancer. Genetic and hereditary factors—such as von Hippel-Lindau disease, papillary renal cell

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carcinoma, and hereditary renal oncocytoma (benign kidney tumors)—may increase the risk of kidney cancer. Other risk factors are advancing age, pre-existing kidney disease, and sex; men are twice as likely as women to be affected (ACS, 2001g; NCI, 2002t).

Epidemiologic Studies of Exposure to Insecticides

A number of studies have examined the increased risk of urologic cancers—including bladder, kidney, prostate, and testicular cancer—among farmers and agricultural workers, but very few have examined the risk in relation to specific insecticides or to insecticides in general. The studies that have been able to investigate specific insecticide exposures often rely on small numbers of exposed cases and cannot validate the exposure.

Prostate Cancer

Only one insecticide exposed case of prostate cancer was found in the Italian chemical production plant cohort noted above (SMR = 1.01, 90% CI = 0.05–4.79) (Rapiti et al., 1997) for exposure to insecticides. A PMR study of farmers identified with death certificates in Wisconsin found an association between prostate cancer and a surrogate of exposure to insecticides based on agricultural activity in the farmers' county (Saftlas et al., 1987). However, the lack of direct exposure measures at the individual level and the use of a PMR analysis, in which high or low ratios for some causes of death may result from decreases or increases in the numbers of deaths from other causes, are limitations of this study. Finally, an ecologic study by Mills (1998) found mixed correlations by ethnicity between age-adjusted incidences of prostate cancer and use of specific pesticides including diazinon, in California.

Testicular Cancer

Hardell and colleagues (1998) conducted a case–control study of testicular cancer among men 30–75 years old and diagnosed in 1989–1992 in the northern and middle parts of Sweden. The 148 cases and 314 population controls were given self-administered comprehensive questionnaires regarding occupational exposures and histories, including exposure to insect repellents and insecticides. Use of insecticides in general revealed no association with testicular cancer (OR = 0.7, 95% CI = 0.4–1.4); an increase in risk was observed for insect repellents (OR = 1.7, 95% CI = 1.03–2.8), most of which have DEET as their active ingredient.

The authors conducted both univariate and multivariate analyses on exposure to insect repellents for less than 115 days versus 115 days or more. It appears that the authors included use of video display units, the occupation of plastics worker, and polyvinylchloride exposure with insect repellent use in the model, although it is not explicitly stated. An increased risk of testicular cancer was associated with both categories of exposure in both the univariate and multivariate analyses; larger estimates of effect were associated with exposure to insect repellents for at least 115 days ($OR_{univariate}$ = 2.3, 95% CI = 1.2–4.4; $OR_{multivariate}$ = 2.1, 95% CI = 1.1–4.2). There may be a potential for recall bias, but it seems unlikely, because relative risks for many of the exposures under study were not increased. A weakness of the findings, however, is that the study authors did not explain whether the exposure occurred within 1 year (rate) or over a lifetime (cumulative). Additionally, the

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authors did not state how they got the information and why 115 days was set as the threshold.

An ecologic study by Mills (1998) found no correlation between age-adjusted incidence of testicular cancer and specific pesticide use, including diazinon, in California.

Bladder Cancer

Rapiti and colleagues (1997) studied risk factors for a number of cancers in a cohort of 505 male workers at an Italian chemical production plant. A worker was considered exposed to insecticides if he had ever worked in the insecticide production process. On the basis of three exposed cases of bladder cancer, an SMR of 3.53 (90% CI = 0.96–9.12) was observed for exposure to insecticides. The extremely small number of exposed cases and the lack of verifiable individual exposure data limit the value of the findings of this study and do not provide the committee with evidence of an association.

Kidney Cancer

Mellemgaard and colleagues (1994) conducted a case–control study on the possible occupational risk factors associated with kidney cancer. Histologically confirmed cases (n = 365) were identified through the Danish Cancer Registry and matched on sex and age to controls (n = 396) from the Central Population Register. Study participants were interviewed in their homes to determine lifetime occupation and exposure histories. Risk of kidney cancer was increased in men (OR = 2.2, 95% CI = 0.8–6.3) and women (OR = 5.7, 95% CI = 0.6–58) who reported insecticide exposure of at least 1 year's duration occurring 10 years or more earlier. An increased risk of kidney cancer—adjusted for age, body mass index, and smoking—was observed among men who reported exposure to insecticides or herbicides for less than 20 years (OR = 1.3, 95% CI = 0.4–4.1) and for 20 years or more (OR = 3.9, 95% CI = 1.0–15.0). The authors indicated that the potential for recall bias was negligible. The risk of kidney cancer was increased with increasing years of exposure to insecticides or herbicides, on the basis of a small number of exposed cases; however, the exposures included exposure to herbicides, which cannot be separated from insecticide exposure.

Urologic Cancers

Several studies examine the relationship between pesticide exposure and urologic cancers. These studies did not contribute substantially to the committee's conclusions because of the lack of specificity of exposure to insecticides and the use of job title as a surrogate of exposure. The studies on pesticide exposure and the risk of urologic cancers include: Alavanja et al., 1987; Aronson et al., 1996; Cantor and Booze, 1991; Dich and Wiklund, 1998; Fincham et al., 1992; Fleming et al., 1999a,b; Schlehofer et al., 1995; Sharpe et al., 2001; Viel and Challier, 1995; Wang and MacMahon, 1979; Wesseling et al., 1999; and Wiklund et al., 1989.

Summary and Conclusion

The body of literature on individual urologic cancers and exposure to insecticides is small and mostly includes studies of exposure to insecticides in general. Only one study focused on a specific product, the insect repellent DEET. Furthermore, for each urologic cancer, there is no more than one study that provides primary evidence for a conclusion, and

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these studies involve small numbers of exposed cases. Table 5.7 identifies the key studies reviewed by the committee for each cancer type—prostate, testicular, bladder, and kidney—and exposure to insecticides.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and prostate, testicular, bladder, and kidney cancers.

TABLE 5.7 Selected Epidemiologic Studies—Urologic Cancers and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Prostate Cancer:			
Insecticides			
Cohort Study—Mortality			
Rapiti et al., 1997	Male workers in Italian chemical production plant	1	1.01 (0.05–4.79)[a]
Testicular Cancer:			
Specific Insecticides			
Case–Control Study			
Hardell et al., 1998	Residents of Sweden		
	Insect repellent (DEET)	39	1.7 (1.03–2.8)
	Univariate analysis		
	1–115 days	NA	1.2 (0.6–2.5)
	≥115 days	NA	2.3 (1.2–4.4)
	Multivariate analysis		
	1–115 days	NA	1.1 (0.6–2.3)
	≥115 days	NA	2.1 (1.1–4.2)
Insecticides			
Case–Control Study			
Hardell et al., 1998	Residents of Sweden	12	0.7 (0.4–1.4)
Bladder Cancer:			
Insecticides			
Cohort Study—Mortality			
Rapiti et al., 1997	Male workers in Italian chemical production plant	3	3.53 (0.96–9.12)[a]
Kidney Cancer:			
Insecticides			
Case–Control Study			
Mellemgaard et al., 1994	Renal cell carcinoma cases in Denmark		
	Insecticide exposure		
	Males	11	2.2 (0.8–6.3)
	Females	3	5.7 (0.60–58.0)
	Insecticide/herbicide exposure		
	Males	7	1.3 (0.4–4.1)
	<20 years	10	3.9 (1.0–15.0)
	≥20 years		
	Females	2	0
	<20 years	2	2.3[b]
	≥20 years		

NOTE: NA = not available.
[a]90% CI
[b]Risks of cancer at specific site for category of high pesticide use versus category of low pesticide use.

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BRAIN AND OTHER CENTRAL NERVOUS SYSTEM TUMORS

Brain and other central nervous system (CNS) tumors (ICD-9 191.0–191.9, 192.0–192.3, 192.8–192.9) are among the most deadly adult cancers (ACS, 2002a). Prognosis and treatment depend heavily on the location of the tumor in the CNS and the type of cell in which it develops. Survival rates vary with age. The 5-year relative survival rate of people 15–44 years old is close to 55%. Those 45–64 years old, however, have a 5-year survival rate of 16%, and those over 65 years old have a 5-year survival rate of 5%.

Histologic types of brain and other CNS cancers in the United States vary in their incidence and mortality by age, sex, and race. Rates are higher in males than in females, and whites have higher rates than blacks, followed by Hawaiians, Chinese, Japanese, and Filipino Americans, and Alaskan natives. Age-specific incidences show a peak under the age of 10 years, an exponential rise from the early 20s to 70 years, and then a decline with increasing age thereafter (Inskip et al., 1995).

The only established environmental risk factor for the development of brain and CNS cancers is exposure to radiation, which usually occurs during treatment for other cancers. Other people at risk include those with impaired immune systems or those with a family history of such disorders as neurofibromatosis type 2, tuberous sclerosis, and Von Hippel-Lindau disease. However, the risk factors for brain and CNS cancers remain largely unknown (ACS, 2002f; NCI, 2002u).

Epidemiologic Studies of Exposure to Insecticides

As pointed out by others (Blair and Zahm, 1995; Bohnen and Kurland, 1995), a major limitation in investigation of insecticides and brain cancer risk has been that most of the studies lack information regarding agents of exposure. Often, no specific exposure determination is undertaken, and analyses are based on job title or industry, such as farmer or agriculture. Another limitation is that many studies relied on death certificates to identify both exposure and disease (as reviewed by Khuder et al., 1998), and pathologic confirmation of the specific type of cancer is lacking. Brain and other CNS cancers can take many forms (such as meningioma, anglioblastoma, astrocytoma, and ganglioglioma), and most epidemiologic studies do not identify the histologic type, because of the lack of pathologic review. As a result, studies often analyze the broader category of "brain or CNS cancers." Epidemiologic studies of brain and other CNS cancers must also address and consider the relatively low survival rate that limits the number of cases to interview and the aggressive nature of the disease, which adversely affects memory and the recall ability of patients. The key studies reviewed by the committee are discussed below, and relevant results are included in Table 5.8.

An ecologic study by Mills (1998) found no correlation between age-adjusted incidences of brain cancer and specific insecticide use, including diazinon, for all 58 California counties. The greatest limitation of this study is the lack of individual measurement of exposure and outcome, as well as the lack of information on other exposures and confounding variables, which could provide alternative explanations for the findings.

A few studies have examined the relationship between insecticide use and brain and other CNS cancers among farmers and agricultural workers. However, most studies are

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limited by the lack of specific and validated exposure information, small numbers of exposed cases, potential recall bias in interview studies, and lack of control for potential confounding by other exposures. Morrison and colleagues (1992) conducted a cohort mortality study of 156,242 male Canadian prairie farmers in 1971–1987 and found an increase in brain cancer among farmers who treated their lands (150 or more acres) with insecticides. However, the exposure information was based on self-reports from proxies or next of kin and the number of brain cancer deaths observed in this population was extremely small ($n = 5$).

A hospital-based case–control study by Musicco and colleagues (1988) in Milan, Italy, reported an increased risk of brain gliomas among those who used insecticides and fungicides (relative risk [RR] = 2.1, 95% CI = 1.27–3.58) compared with nonglioma brain tumor controls. Results were similar when the total control population (tumor controls and neurologic controls) was used for the comparison (RR = 2.0, 95% CI = 1.22–3.23). However, exposure information was based on self-reports, and the use of insecticides cannot be separated from the use of fungicides, which are not a part of the committee's review.

Another case–control study evaluated the relationship between all CNS cancers and exposure to insecticides and fungicides. On the basis of death certificates from 24 US states, Cocco and colleagues (1998c) found that agricultural exposure to pesticides other than herbicides was associated with an increased risk of CNS cancer among white women (OR = 1.4, 95% CI = 1.0–1.8) and white men (OR = 1.3, 95% CI = 1.2–1.4). Controls were selected from subjects who died from nonmalignant diseases, excluding neurologic disorders. Industrial hygienists reviewed the occupation and industry combinations presented on the death certificates and developed a job–exposure matrix in which each combination was assigned a binary exposure value (exposed or unexposed). In their later analyses of the same dataset with a more detailed job–exposure matrix, in which each occupation–industry combination was assigned to one of four probability and intensity levels of exposure, the authors (Cocco et al., 1999b) again found an increased risk of CNS cancer among women (OR = 1.3, 95% CI = 1.1–1.5). However, there was no clear pattern of CNS cancer risk with increasing probability or intensity of exposure to insecticides and fungicides. Furthermore, the studies were not able to separate the specific role of insecticide exposure versus fungicide exposure and the risk of CNS cancer in this population.

Several studies examined the relationship between exposure to pesticides in general and brain and other CNS cancers among various occupationally exposed populations. Although several studies demonstrate an increase in brain and other CNS cancers, including studies of nonwhite farmers in North Carolina (Delzell and Grufferman, 1985), farmers in Sweden (Rodvall et al., 1996), and women in China (Heineman et al., 1994), the exposure information is based on self-reports, and the studies are not able to identify the specific agent responsible for the cancer risk increase. Issues of exposure misclassification, potential recall bias, and lack of control for confounding variables limit the value of these studies for drawing a conclusion. Studies on pesticide applicators and farmers licensed to use pesticides also found an increased risk of brain and other CNS cancers but used job titles as surrogates of exposure to pesticides (Alberghini et al., 1991; Corrao et al., 1989; Figa-Talamanca et al., 1993b; Godon et al., 1989; Pesatori et al., 1994; Viel et al., 1998; and Wiklund et al., 1989). The lack of specific information on exposure to insecticides limits the usefulness of these findings for the purposes of this report.

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Summary and Conclusion

A number of epidemiologic studies have examined the relationship between brain and other CNS cancers and exposure to pesticides in general, but there is a paucity of evidence to determine whether insecticides or the specific insecticides that are the subject of the committee's review were responsible for the observed increases in risk, especially among pesticide applicators, farmers, and agricultural workers. Those occupational groups are exposed to a multitude of chemicals other than insecticides, depending on the nature of their work, including organic dusts, solvents, other agricultural chemicals, fuels and engine exhausts, and infectious microorganisms. Table 5.8 identifies the body of literature reviewed and the relevant findings.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and brain and other central nervous system cancers.

TABLE 5.8 Selected Epidemiologic Studies—Brain and Other CNS Tumors and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Insecticides			
Cohort Study			
Morrison et al., 1992	Canadian prairie farmers	5[a]	1.34 (0.55–3.25)
Case–Control Studies			
Cocco et al., 1999b	Female CNS deaths in 24 US states		
	Insecticides and fungicides	210	1.3 (1.1–1.5)
Cocco et al., 1998c	CNS deaths in 24 US states		
	Pesticides other than herbicides		
	White men	1079	1.3 (1.2–1.4)
	White women	62	1.4 (1.0–1.8)
Musicco et al., 1988	Brain glioma patients in Milan, Italy		
	Insecticide and fungicide users	37	2.1 (1.27–3.58)

[a]Prairie farmers who treated at least 150 acres with insecticides.

NON-HODGKIN'S LYMPHOMA

Cancers that originate in the lymphoid tissues—which include the lymph nodes, spleen, thymus, tonsils and adenoids, and bone marrow—are classified as lymphomas and account for about 5% of all new cancer cases in the United States. Lymphomas are divided generally into two categories according to cell histology: Hodgkin's disease (discussed in the next section) and non-Hodgkin's lymphoma (NHL), which includes all other types of lymphomas.

The incidence of NHL (ICD-9 200.0–200.8, 202.0–202.2, 202.8–202.9) has nearly doubled since the early 1970s but has stabilized among most demographic groups. The average age at diagnosis is the early 40s, but the incidence continues to increase dramatically with age, with the elderly at highest risk. Survival varies according to the

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specific type of lymphoma; the average 5-year survival rates range from 30% to over 70% (ACS, 2002g).

Men have slightly higher incidences than women, and whites are affected more often than blacks or Asian Americans. In addition to age and race, risk factors for NHL include undergoing radiation therapy or chemotherapy for other cancers and a weakened immune system because of autoimmune disease, genetic immune deficiency, or use of immunosuppressant drugs. Infections with the human T-cell leukemia/lymphoma virus, human immunodeficiency virus, *Helicobacter pylori* bacteria, malaria, and the Epstein–Barr virus are also considered to be risk factors (ACS, 2002g; NCI, 2002v).

Epidemiologic Studies of Exposure to Insecticides

The relationship between agriculture-related occupations and NHL has been examined for many years. A number of well-conducted studies have focused on specific risk factors related to agricultural work, including use of insecticides and herbicides. The key studies reviewed by the committee are described below and summarized in Table 5.9.

The potential for increased risk of NHL with exposure to specific organophosphorous insecticides has been examined in several studies. The studies were generally case–control studies in which participants were interviewed about various types of pesticide use. Cantor and colleagues (1992) were among the first to use case–control studies to investigate the relationship between specific insecticides and NHL. Their subjects were 622 white men with NHL in Iowa (1981–1983) and Minnesota (1980–1982); NHL diagnosis was histologically confirmed. The authors interviewed cases and population-based controls, or close relatives or friends of deceased or incompetent subjects, to determine exposure to specific pesticides, including 23 animal insecticides and 34 crop insecticides. Although use was separated by crop or animal application, most of the agents were used on both.

NHL risk increased with the use of several agents; however, risk was not increased for ever handling dichlorvos and various other insecticides that were not considered in this report. Risk of NHL increased with the use of malathion as an animal or crop insecticide; and the risk was also greater for each type of application when exposure occurred without the use of protective equipment ($OR_{animal\ insecticide}$ = 1.4, 95% CI = 0.8–2.2; $OR_{crop\ insecticide}$ = 1.9, 95% CI = 0.9–4.1). Use of carbaryl on crops without personal protective equipment was also associated with increased NHL risk (OR = 2.2, 95% CI = 1.2–4.2). For several of the insecticides studied, use before 1965 resulted in higher risk estimates for NHL: malathion (OR_{crops} = 2.9, 95% CI = 1.1–7.4), diazinon (OR_{crops} = 2.6, 95% CI = 1.2–5.9) and carbaryl (OR_{crops} = 3.8, 95% CI = 1.1–13.6). The overall positive findings might indicate either a longer exposure timeframe or an adequate latency period for the development of lymphoma.

Risk of NHL was also associated with ever handling lindane as an animal insecticide (OR = 1.4, 95% CI = 1.0–2.1) and using it as a crop insecticide (OR = 2.0, 95% CI = 1.0–3.7). In supplemental interviews, Iowa farmers were asked about the number of days per year that they had used the insecticides. The resulting analysis did not show a trend of increased risk with increased use of lindane (1–4 days/year, OR = 3.3; 5–9 days/year, OR = 0.4; 10 or more days/year, OR = 0.5), but this was based on small numbers of exposed cases (Cantor et al., 1993).

Although the authors conducted multiple comparisons in the study of Iowa and Minnesota cases, there was an increase in NHL risk with exposure to a number of insecticides. ORs were adjusted for vital status, age, state, cigarette smoking, family history

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of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis (OR > 1.5). Exposure misclassification is a potential limitation of the study because of the high proportion of proxy respondents (28.9% of cases and 34.2% of controls), but, if nondifferential misclassification exists, it would bias the results to show no association.

Blair and colleagues (1998) pooled data from population-based case–control studies of NHL among white men in Kansas (Hoar et al., 1986), Nebraska (Zahm et al., 1990), and Iowa and Minnesota (Cantor et al., 1992) to investigate the association with exposure to lindane in greater detail than in the original studies while controlling for potential confounders, including other insecticides or herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D). Some 987 cases of NHL and 2895 population-based controls participated in the study and provided information on exposure to lindane, farm practices, and use of other agricultural chemicals through telephone interviews. Compared with nonfarmer controls, risk of NHL was increased in farmers who ever used lindane (OR = 1.5, 95% CI = 1.1–2.0); the risk was similar if use began more than 20 years before lymphoma diagnosis (OR = 1.7, 95% CI = 1.1–2.5). The findings were adjusted for age, proxy or direct interview, and state of residence but not for other pesticide use. Increased risk of NHL with lindane use was observed whether or not subjects wore protective equipment when lindane was used for fewer than 4 days/year and when it was used on more than 4 days/year. When exposures to carbaryl, diazinon, carbamates, and organophosphorous insecticides were controlled for in the analysis, the relative risk of NHL with lindane use was 1.2 to 1.5. Although the methodologies of the three case–control studies pooled are similar, differences may limit the interpretation of this study; but the study authors do not consider such differences in their discussion. Another limitation of this study is the use of proxy respondents; the risk of lindane use was higher in subjects with proxy respondents than in index subjects, and this suggests differential misclassification.

Zheng and colleagues (2001) further examined the pooled NHL data to look for any effect of carbamate pesticides on NHL risk with particular attention to carbaryl (Sevin). Exposure to carbaryl was ascertained through interviews with study participants or proxies, regarding exposure to carbaryl from farm use, personal handling, and length and frequency of use. Risk of NHL was increased with personal handling (OR = 1.8, 95% CI = 1.1–2.8), farm use (OR = 1.6, 95% CI = 1.0–2.4), use on less than 5 days/year (OR = 2.4, 95% CI = 1.0–5.9), and use on 5 or more days/year (OR = 1.5, 95% CI = 0.3–10.0). Analyses adjusted for age, type of respondent (proxy or index subject), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, tobacco smoking, and exposure to other pesticides. Risk of NHL was also increased with 20 years or more since carbaryl exposure and with increasing duration of exposure.

Unlike some of the studies of insecticides and NHL, the Zheng study (2001) attempted to control for confounding by other pesticides. The authors indicated that they reached the same conclusions when limiting analyses to index respondents only; that indicates that the potential for recall bias was low. The lack of verified exposure information and the presence of nonoccupational sources of exposure are limitations of the study. However, the response rate was high, the sample was large, and possible confounders—such as exposure to other insecticides or pesticides, smoking, and family history of cancer—were controlled for in the analysis.

A case–control study conducted by Hardell and Eriksson (1999) included cases of NHL, 25 years old or older, and diagnosed in 1987–1990 in seven northern and middle

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counties of Sweden. Comprehensive questionnaires were administered to 404 cases and 741 controls and followed up with supplemental telephone interviews. To decrease the potential for recall bias, deceased controls were used for deceased cases. Increased NHL risk was associated with exposure to pyrethrin (OR = 1.3, 95% CI = 0.5–3.4). Because only a univariate analysis was conducted for insecticides, confounding by other pesticides or agents cannot be ruled out. The large number of cases and the use of detailed questionnaires to estimate exposures are strengths of this study.

In a followup study of workers in the grain and flour industry, flour millers with more than 20 years of followup since first employment demonstrated an age-adjusted increased risk of NHL mortality (SMR = 2.31, 95% CI = 1.19–4.04) (Alavanja et al., 1990). Exposure to malathion was inferred from records and questionnaires. A nested case–control study of 21 cases of NHL in this cohort study found that the NHL risk increased with duration of followup since first employment in flour mills, from an OR of 1.5 (95% CI = 0.2–13.9) for those followed less than 15 years to an OR of 9.4 (95% CI = 1.4–61.5) for workers followed for 25 years or more. Work histories were available for only a small proportion of the cases and controls, and this limited the analyses by department and job. Also, the number of NHL cases in the cohort was small.

Most studies on agricultural chemical use and NHL risk have focused on men. Zahm and colleagues (1993) conducted a case–control study of the risk of NHL and exposure to insecticides among female agricultural pesticide workers in 66 counties in Nebraska. Increased risk of NHL was observed for diazinon ($OR_{use\ on\ farms}$ = 1.9; $OR_{personal\ handling}$ = 4.1), malathion ($OR_{use\ on\ farms}$ = 1.9; $OR_{personal\ handling}$ = 3.6), lindane ($OR_{use\ on\ farms}$ = 1.8), and carbaryl ($OR_{use\ on\ farms}$ = 2.6). All ORs were adjusted for age. Limitations of the study include the small number of exposed cases and the lack of information on activities most likely to result in exposure to the agents of concern among women.

Studies reviewed but not considered primary evidence in drawing conclusions included a PMR study among grain-industry workers who were probably exposed to malathion (Alavanja et al., 1987) and an ecologic study previously described, which correlated cancer rates, including NHL, with the number of pounds of diazinon used in California (Mills, 1998). Those studies are limited by the lack of individual exposure measurement and other characteristics of their designs, as discussed in Chapter 2.

Weisenburger (1990) conducted a case–control study of men in eastern Nebraska to examine the effect of agricultural exposure on NHL risk. Histologically confirmed NHL cases (n = 201) and population-based controls (n = 725) were interviewed by telephone to determine individual exposure to specific agricultural chemicals. On the basis of self-reported exposure, several classes of insecticides were associated with increased risk of NHL among men, including organophosphorous insecticides (OR = 1.9, 95% CI = 1.1–3.1). Recall bias and confounding by other pesticides and unidentified exposures are limitations of this study.

Using the Centers for Disease Control and Prevention Selected Cancers Study, Tatham and colleagues (1997) identified NHL cases in eight population-based registries in Atlanta, Connecticut, Iowa, Kansas, Miami, San Francisco, Detroit, and Seattle. Cases (n = 1048) were diagnosed in 1984–1988 and confirmed by pathologic slide review. Controls (n = 1659) were enrolled with random-digit dialing and were matched on registry location and age. No increased NHL risk was observed for exposure to organophosphorous insecticides (OR = 0.66, 95% CI = 0.43–1.00), carbamates (OR = 0.93, 95% CI = 0.56–1.50), or

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pyrethroids (OR = 0.52, 95% CI = 0.14–1.90). Although the committee reviewed the relevant data points for all NHL cases combined, the primary focus of the Tatham study was risk factors related to different groups of NHL subtypes. The authors concluded that the lack of positive findings may indicate that the subgroups chosen are not etiologically distinct.

Several of the studies described above for specific insecticides also found NHL risk increased with exposure to classes of insecticides. Cantor and colleagues (1992) found an association between NHL and use of organophosphorous insecticides on crops or animals (OR = 1.5, 95% CI = 1.1–2.0), as did Zahm and colleagues (1993) with organophosphorous insecticides use on farms (OR = 1.2, 95% CI = 0.6–2.5). The association was stronger for personal handling of organophosphorous agents (OR = 4.5, 95% CI = 1.1–17.9).

NHL risk associated with use of carbamates (OR = 1.1, 95% CI = 0.8–1.7) was evaluated in the study by Cantor and colleagues (1992) described earlier; however, the study by Zahm and colleagues (1993) did not include enough cases exposed to carbamates to derive any estimated risk. Increased NHL risk was found in the study of men in eastern Nebraska exposed to carbamates (OR = 1.8, 95% CI = 1.0–3.2) (Weisenburger, 1990) and in the study by Zheng and colleagues (2001) of farmers who reported using carbamates as an insecticide (OR = 1.6, 95% 1.2–2.2), as described above.

A study by Nanni and colleagues (1996) of combined cases of chronic lymphocytic leukemia (CLL) and NHL in a population-based case–control study in agricultural areas in Italy reported an increased risk of low-grade NHL and CLL (combined) with exposure to carbamates (OR = 3.08, 95% CI = 1.05–9.0). However, the value of the study's findings is limited in that it combines two types of cancer cases that may have different risk factors and etiologies.

Several studies have examined the risk of NHL with exposure defined to encompass insecticides in general. The role of farm use of insecticides in the development of NHL and other diseases was examined by Hoar and colleagues (1986), who conducted a case–control study of 200 white men living in Kansas and diagnosed with NHL in 1979–1981. Cases were histologically confirmed. Three population-based controls, matched for age and vital status, were selected for each case. Insecticide use of greater than 3 days/year and adjusted for herbicide use showed an increase in NHL risk (OR = 1.4, 95% CI = 0.6–3.1). Exposure misclassification in this study resulting from vague questions concerning agents and errors in recall by the study subjects were likely to affect cases and controls in a similar manner.

Use of any insecticides on farms by female pesticide workers (study described above) showed a slightly decreased risk of NHL (OR = 0.8, 95% CI = 0.5–1.3), whereas personal handling of insecticides resulted in an increased risk (OR = 1.3, 95% CI = 0.7–2.3) (Zahm et al., 1993).

Scherr and colleagues (1992) reported on 303 cases of NHL diagnosed in 1980–1982 in the Boston metropolitan area; cases were histologically confirmed. Population-based controls were matched to cases on age and sex and interviewed directly or by proxy regarding exposure to agricultural chemicals. Among those reporting exposure to pesticides or insecticides, risk of NHL was increased (OR = 1.8, 95% CI = 0.9–3.7). However, the study is limited by the inclusion of exposure to pesticides in general and insecticides combined. Other studies with similarly broad exposure measures had inconsistent findings regarding NHL risk (Hardell and Eriksson, 1999; Settimi et al., 1999; Zhong and Rafnsson, 1996).

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Using death certificates to identify occupation and cases of NHL and other causes of death to use as controls, Cantor (1982) considered people listed as farmer to have been exposed to insecticides. NHL risk was increased in the 15 counties with highest insecticide use (OR = 2.4, 95% CI = 1.04–5.7) and to a smaller extent in all other counties (OR = 1.53, 95% CI = 1.00–2.3). The study is limited by its indirect and nonspecific exposure determination and by the use of death certificates for identifying cause of death and the use of occupation as a surrogate of exposure.

The potential relationship between working in agriculture or other occupations related to pesticides in general and increased risk of NHL has been examined in a number of studies. The studies provide supportive information for the discussion of insecticide exposure, but the agents measured were broadly defined.

Mortality studies investigating deaths from NHL among occupational groups likely to be exposed to pesticides, such as farmers and agricultural workers, have yielded inconsistent findings (e.g., Alavanja et al., 1988; Kross et al., 1996; Littorin et al., 1993; Ritter et al., 1990; Sathiakumar et al., 1992; Sperati et al., 1999). Studies of the incidence of NHL have also found mixed results among farmers and other populations likely to be exposed to pesticides in general (e.g., Corrao et al., 1989; Hansen et al., 1992; Waterhouse et al., 1996; Wiklund and Dich, 1994, 1995; Wiklund et al., 1989; Zahm, 1997).

Several case–control studies have examined the relationship between NHL and exposure defined as farming or pesticide use. Many of these studies have found a positive association between employment in such occupations or agricultural groups and NHL (e.g., Balarajan, 1988; Brownson and Reif, 1988; Burmeister et al., 1983; Cantor, 1982; Costantini et al., 2001; Pasqualetti et al., 1991; Pearce et al., 1985, 1987); other published case–control studies found no relationship between pesticide-associated occupations and NHL (e.g., Franceschi et al., 1989; Fritschi and Siemiatycki, 1996; Schumacher and Delzell, 1988).

Although those studies of pesticide users provide supportive data, no specific insecticide or class of insecticides can be implicated from such broadly defined surrogate exposure measures. In general, the studies could not measure the numerous potential confounders of pesticide-related occupations, including fuel emissions from agricultural equipment, herbicides or fungicides, or a number of other chemicals. Many studies appear to support a relationship between NHL and herbicide exposures, but there is a great potential for confounding between insecticide and herbicide use.

Summary and Conclusion

A number of well-conducted case–control studies show an increased NHL risk associated with exposure to specific organophosphorous and carbamate insecticides respectively. By design, such studies assign specific exposures to individual subjects albeit without direct workplace or environmental measurements; in these studies, increased risks were observed with exposure to organophosphorous agents and carbamates in general and malathion, diazinon, lindane, and carbaryl exposure in particular. However, there are too few studies with exposure measurements at the individual insecticide level to draw conclusions on any specific insecticide. The increase in risk estimates, especially those related to organophosphorous insecticides and carbamates, lend support to a possible association. Those associations are consistently increased across various categorizations of the type of use or the source of the exposure information (self-report or proxy respondent). In addition, the studies that have examined insecticide and pesticide use in general have

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shown increased NHL risks. The potential for downward bias resulting from a healthy worker effect inherent in studies with occupationally exposed cases and population controls also underscore the positive results. Table 5.9 identifies the critical studies reviewed by the committee and the relevant data used in drawing its conclusion.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to organophosphorous insecticides or to carbamates and non-Hodgkin's lymphoma.

TABLE 5.9 Selected Epidemiologic Studies—Non-Hodgkin's Lymphoma and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific Insecticides			
Case–Control Studies			
Zheng et al., 2001	Pooled analysis of NHL cases		
	Carbaryl (farm use based on all subjects)	45	1.6 (1.0–2.4)
	Carbaryl (farm use based on all subjects, adjusted for other pesticides)	45	1.4 (0.9–2.2)
Hardell and Eriksson, 1999	Residents of northern and middle Sweden		
	Pyrethrins	10	1.3 (0.5–3.4)
Blair et al., 1998	Pooled analysis of NHL cases		
	Lindane (used by farmer, index respondents)	93	1.5 (1.1–2.0)
Zahm et al., 1993	Female residents of eastern Nebraska		
	Diazinon (farm use)	7	1.9
	Diazinon (personally handled)	2	4.1 (0.4–43.2)
	Malathion (farm use)	9	1.9
	Malathion (personally handled)	3	3.6 (0.5–23.9)
	Carbaryl (farm use)	5	2.6
	Lindane (farm use)	5	1.8
Cantor et al., 1992	Residents of Iowa and Minnesota, ever handled:		
	Diazinon (crop insecticide)	27	1.5 (0.9–2.5)
	Dichlorvos (animal insecticide)	20	1.2 (0.7–2.2)
	Malathion (animal insecticide)	43	1.3 (0.9–2.1)
	Malathion (crop insecticide)	21	1.5 (0.8–2.7)
	Carbaryl (crop insecticide)	21	1.7 (0.9–3.1)
	Lindane (animal insecticide)	55	1.4 (1.0–2.1)
	Lindane (crop insecticide)	21	2.0 (1.0–3.7)
	Dichlorvos (animal insecticide)	20	1.2 (0.7–2.2)
Classes of Insecticides			
Case–Control Studies			
Zheng et al., 2001	Pooled analysis of NHL cases		
	Carbamates (insecticide use based on all subjects)	89	1.6 (1.2–2.2)
Tatham et al., 1997	CDC Selected Cancers Study		
	Organophosphorous agents	37	0.66 (0.43–1.00)
	Carbamates	27	0.93 (0.56–1.50)
	Pyrethroids	3	0.52 (0.14–1.90)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Zahm et al., 1993	Female residents of eastern Nebraska		
	Carbamates (farm use)	7	1.6 (0.6–4.4)
	Organophosphorous agents (farm use)	14	1.2 (0.6–2.5)
	Organophosphorous agents (personally handled)	6	4.5 (1.1–17.9)
Cantor et al., 1992	Residents of Iowa and Minnesota, ever handled:		
	Organophosphorous agents (either use)	96	1.5 (1.1–2.0)
	Carbamates (crop or animal)	43	1.1 (0.8–1.7)
Weisenburger et al., 1990	Male residents of eastern Nebraska		
	Organophosphorous agents	NA	1.9 (1.1–3.1)
	Carbamates	NA	1.8 (1.0–3.2)
Insecticides			
Case–Control Studies			
Hardell and Eriksson, 1999	Residents of northern and middle Sweden		
	Insecticides	90	1.2 (0.8–1.7)
Zahm et al., 1993	Female residents of eastern Nebraska		
	Insecticides (farm use)	56	0.8 (0.5–1.3)
	Insecticides (personally handled)	22	1.3 (0.7–2.3)
Hoar et al., 1986	Residents of Kansas		
	Insecticides (adjusted for herbicide use)		
	3+ days/year	14	1.4 (0.6–3.1)

NOTE: NA = not available.

HODGKIN'S DISEASE

Hodgkin's disease (HD) (ICD-9 201.0–201.9) differs from NHL in cellular origin and can be identified by the presence of Reed-Sternberg cells in biopsied tissue. HD is far less common than NHL (ACS, 2002a). In the United States, incidence and mortality have been decreasing since the early 1970s, and the 5-year survival rate has increased to 82%. The highest rates of HD are found among persons 15–35 years old and over 55 years old. People infected with the Epstein-Barr virus or having weakened immune systems seem to be at greater risk for HD. Some cases in which members of the same family have developed HD suggest a genetic predisposition, common environmental exposures, or both, but no major risk factors have been discovered (ACS, 2002h; NCI, 2002w).

Epidemiologic Studies of Exposure to Insecticides

Few studies have examined the relationship between HD and exposure to specific insecticides thought to have been used during the Gulf War. The literature reviewed by the committee and its strengths and limitations are discussed below, and relevant results are presented in Table 5.10.

Although the risk of HD has been investigated among farmers, agricultural workers, and others known to be exposed to pesticides, only one case–control study (Zahm and colleagues, 1988) specifically examined the effect of insecticides on the risk of HD. Cases were selected from among white men, 21 years old or older who were diagnosed in 1976–1982 in Kansas. A total of 121 HD cases remained in the analysis after initial diagnosis,

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pathology review and confirmation, and completion of telephone interview. Population-based controls were matched 3:1 on age and vital status. No association with HD was observed for farming-related exposure to general insecticides (OR = 0.8, 95% CI = 0.5–1.4) and animal insecticides (OR = 0.9, 95% CI = 0.5–1.5). Use of crop insecticides also resulted in no excess risk of HD (OR = 1.1, 95% 0.6–1.9). The study is limited by nonspecific exposure information and the possibility of nondifferential misclassification of exposure.

A PMR study by Alavanja and colleagues (1987) examined the risk of lymphatic and hematopoietic malignancies, including HD, among workers in the grain industry; exposure was inferred from employment information, union records, and responses to questionnaires from some of the subjects. On the basis of one death, a PMR of 1.74 was found for HD among all grain-mill workers. However, the lack of individual exposure data and the fact that only one case of HD was observed are limitations of this study. Given the inherent limitations in the design of a PMR study, such results were considered only as supportive evidence.

The possible association between HD and work in agricultural professions has been explored in numerous studies. The studies provide some background for the committee's discussion but do not provide the specificity of exposure to insecticides needed to draw conclusions of association for this review. The relevant mortality studies have had inconsistent findings; increased risk of HD was found in some studies (Alavanja et al., 1988; Balarajan, 1988; Franceschi et al., 1991; Persson et al., 1993; Waterhouse et al., 1996; Wiklund and Dich, 1994, 1995; Wiklund et al., 1989) but not in others (Brownson and Reif, 1988; Costantini et al., 2001; Fritschi and Siemiatycki, 1996; Pearce et al., 1985; Zahm, 1997).

Summary and Conclusion

Most of the relevant studies on HD have characterized exposure broadly and have examined increased risks related to agricultural occupations or pesticides in general. The results, including those of the few studies on insecticide exposure, have been inconsistent with regard to a relationship between exposure to pesticides or insecticides and the risk of HD. There is insufficient evidence to examine the potential effects of exposure to insecticides on this health outcome. Table 5.10 highlights the key study reviewed by the committee and the relevant data considered in drawing its conclusion.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and Hodgkin's disease.

TABLE 5.10 Selected Epidemiologic Studies—Hodgkin's Disease and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Insecticides			
Case–Control Study			
Zahm et al., 1988	Residents of Kansas		
	Insecticides (ever use)	38	0.8 (0.5–1.4)
	Insecticides (crop use)	25	1.1 (0.6–1.9)
	Insecticides (animal use)	32	0.9 (0.5–1.5)

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MULTIPLE MYELOMA

Multiple myeloma (MM) (ICD-9 203.0, 203.2–203.8) is a relatively rare cancer, accounting for only about 1% of all new cancers diagnosed per year in the United States (ACS, 2002a). It is characterized by excessive proliferation and disordered function of plasma cells (a type of white blood cell formed from B-cell differentiation). The causes of MM are not known, but age and race are considered risk factors. Incidence increases dramatically with age; nearly 98% of all new cases occur in people over 40 years old, and MM occurs twice as often in blacks as in whites. Exposure to ionizing radiation, family history of cancer, occupational exposure in petroleum-related industries, and the presence of other plasma cell diseases are other possible risk factors. In many cases, MM does not cause noticeable symptoms until it is well advanced. However, if it is detected in Stage 1 of its development, the 5-year survival rate is about 50% (ACS, 2002i; NCI, 2000).

Epidemiologic Studies of Exposure to Insecticides

There are few studies in the literature of exposure to insecticides and the risk of MM. The studies that were reviewed included small numbers of exposed cases, lacked specific and validated exposure information, and did not control for potential covariates in the analysis. The key studies reviewed by the committee, including the strengths and limitations of the data, are discussed below with results shown in Table 5.11.

A case–control study conducted by Brown and colleagues (1993) examined MM in 173 white males diagnosed in 1981–1984 in Iowa and exposure to a number of insecticides, including malathion, dichlorvos, lindane, and carbaryl. A pathologist confirmed all diagnoses, which were identified through the Iowa Health Registry. To determine past exposures to specific insecticides, the authors interviewed cases (or close relatives) and population-based controls (n = 650) about specific exposure to 24 animal insecticides and 34 crop insecticides. An increased risk of MM was associated with use of dichlorvos (OR = 2.0, 95% CI = 0.8–5.0) as an animal insecticide, malathion (OR = 1.9, 95% CI = 0.8–4.6) as a crop insecticide, and handling, mixing, or applying carbaryl for crop use (OR = 1.5, 95% CI = 0.6–3.9). No risk was observed in persons mixing, handling, or applying malathion as an animal insecticide (OR = 0.8, 95% CI = 0.3–1.9). Although the study shows a slightly increased risk of MM with exposure to a number of specific insecticides, the risk was greater among deceased cases (interviewed by proxy through the closest relatives) than among living cases indicating the potential for recall bias.

Brown and colleagues' study was an expansion of Burmeister's (1990) earlier case–control study on the same set of Iowa males. Although Brown and colleagues were able to identify specific animal and crop insecticides, Burmeister focused on the classes of insecticides. Increased odds ratios were evident for animal and crop use of organophosphorous insecticides (OR = 1.22 and 1.31, respectively) and for carbamates used on crops (OR = 1.83) but not on livestock (OR = 1.00). No association was found between MM and pyrethrins used as livestock insecticides. As in the Brown and colleagues study, small numbers of exposed cases and the potential for differential recall bias between proxy and living cases are limitations.

Nanni and colleagues (1998) conducted a case–control study in the largely agrarian province of Forlì, Italy. The Romagna Cancer Registry was used to identify 46 MM cases

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diagnosed in 1987–1990 for study inclusion. On the basis of three exposed cases, a multivariate analysis revealed a slightly increased risk of MM with exposure to carbamate insecticides (as a class) for those reporting exposure at any point in time and for those who used the insecticides in their profession. Although an *a priori* matrix was used in assessing exposure, which probably reduced recall bias, there is still the potential for nondifferential misclassification of exposure, which would tend to reduce the risk estimate. The authors also stated that the MM diagnosis may have been less accurate among residents who lived farther from the main specialized hospitals in Italy. The small number of exposed cases also limits the value of the findings of this study.

Two studies of MM mortality and occupation as farmer obtained from death certificates in Iowa (Burmeister et al., 1983) and Wisconsin (Cantor and Blair, 1984) used regional production of crops or livestock as the basis of estimating relative amounts of insecticide use by county. Although the risk of MM was increased in both studies in areas where insecticide use was estimated to be high, the committee did not consider those two studies critical in forming their conclusions, because exposure and disease outcome data were based on death certificates only and there was no further specification or validation of exposure or disease status. Furthermore, the exposure estimates used are approximations of county-wide agricultural practices and do not apply to all residents of every county.

Possible sex-related differences in MM risk were examined by Zahm and colleagues (1992) in a case–control study of agricultural exposures in eastern Nebraska. Exposure to insecticides yielded no association in men (OR = 0.6, 95% CI = 0.2–1.4) on the basis of 11 cases, but women experienced an increased MM risk (OR = 2.8, 95% CI = 1.1–7.3) on the basis of 21 cases. The increased MM risk among women is difficult to explain but could have been due to chance or to confounding by other exposures.

The Brown and colleagues study described above found a slightly increased risk of MM among persons reporting exposure to and use of insecticides (OR = 1.2, 95% CI = 0.9–1.8) (Brown et al., 1993).

A number of studies have looked at MM risk among workers potentially exposed to pesticides. Exposures were broadly characterized, and separate analyses are not provided on more relevant exposures of concern, such as exposure to insecticides. Cohort mortality studies (Ritter et al., 1990; Sperati et al., 1999; Viel and Richardson, 1993), incidence studies (Kristensen et al., 1996; Wiklund and Dich, 1994, 1995; Wiklund et al., 1989), and case–control studies (Brownson and Reif, 1988; Costantini et al., 2001; Demers et al., 1993; Eriksson and Karlsson, 1992; Fritschi and Siemiatycki, 1996; Pearce et al., 1985) of MM and exposure to pesticides have shown mixed results. Although some studies show an increased MM risk with pesticide use, they do not evaluate the specific agents of interest needed to draw conclusions for the purposes of this review.

Summary and Conclusion

Several studies that have examined the association between MM risk and exposure to specific insecticides, classes of insecticides, and insecticides in general show small positive associations. However, this body of evidence is limited by the lack of specific or valid exposure determinations, small numbers, and the likelihood that the small associations are due to bias and chance. It is interesting that a number of studies show slight increases in risk; future research to explore the relationship between exposure to insecticides and MM needs additional statistical power—larger numbers of subjects and better measures of

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exposure. Table 5.11 highlights the key studies reviewed by the committee and the relevant data considered in drawing its conclusion.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the insecticides under review and multiple myeloma.

TABLE 5.11 Selected Epidemiologic Studies—Multiple Myeloma and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific Insecticides			
Case–Control Study			
Brown et al., 1993	Male residents of Iowa		
	Dichlorvos (animal use)	7	2.0 (0.8–5.0)
	Lindane (animal use)	16	1.1 (0.6–2.0)
	Lindane (crop use)	5	1.2 (0.4–3.4)
	Malathion (animal use)	6	0.8 (0.3–1.9)
	Malathion (crop use)	8	1.9 (0.8–4.6)
	Carbaryl (crop use)	6	1.5 (0.6–3.9)
Classes of Insecticides			
Case–Control Studies			
Nanni et al., 1998	Residents of Forlí, Italy		
	Carbamates (total exposed)	3	1.2 (0.6–2.3)
	Carbamates (professionals only)	3	1.7 (0.4–6.9)
Burmeister, 1990	Male residents of Iowa		
	Organophosphorous agents (crops)	NA	1.31
	Organophosphorous agents (livestock)	NA	1.22
	Carbamates (crops)	NA	1.83
	Carbamates (livestock)	NA	1.00
	Pyrethrins (livestock)	NA	1.00
Insecticides			
Case–Control Studies			
Brown et al., 1993	Male residents of Iowa		
	Insecticides	91	1.2 (0.9–1.8)
Zahm et al., 1992	Residents of Nebraska		
	Insecticides (male)	11	0.6 (0.2–1.4)
	Insecticides (female)	21	2.8 (1.1–7.3)

ADULT LEUKEMIA

The four main types of leukemia—acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML) (ICD-9 204.0, 204.1, 205.0, 205.1)—are grouped by the developmental pace of the disease and the type of blood cell affected. Therefore, the disease can be either acute or chronic and can affect either myeloid or lymphocytic cells (ACS, 2002j).[3]

[3] The ICD codes for all types of leukemia include ICD-9 202.4, 203.1, 204.0–204.9, 205.0–205.9, 206.0–206.9, 207.0–207.2, 207.8, 208.0–208.9.

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AML is the most common type of leukemia in adults; it is evenly distributed between sexes and occurs in both adults and children, but CLL almost never occurs in children. CML is mostly limited to adults and is the third most common type of leukemia. ALL, the most common form of leukemia in children, accounts for the smallest number of adult cases of leukemia (ACS, 2002a; NCI, 2002x). (Conclusions regarding exposure to insecticides and childhood cancers are discussed at the end of this chapter.) A fifth type of leukemia—hairy cell leukemia (HCL) (ICD-9 202.4)—is similar to CLL in that it is a slowly progressing cancer of the lymphocytes. However, because the cells have a different morphology, HCL is often considered separately. Accounting for an estimated 2% of all leukemia cases diagnosed in adults each year, HCL most often affects adults over 50 years old (ACS, 2002j).

Overall, the 5-year survival rate of leukemia patients is 44%—a rate that has tripled in the last 40 years. The survival rates for the types of leukemia differ markedly: 14% for AML, 32% for CML, 58% for ALL, and 71% for CLL. Leukemia is known to be associated with exposure to benzene, high doses of radiation, chemical drugs used to treat other cancers, and smoking. One factor currently under investigation is exposure to electromagnetic fields. However, none of those exposures can explain the majority of leukemia cases diagnosed each year. Rare inherited diseases—such as Fanconi's anemia, Wiskott-Aldrich syndrome, Bloom's syndrome, Li-Fraumeni syndrome, Down's syndrome, and ataxia telangiectasia—also increase the risk of acute leukemia (ACS, 2002j; NCI, 2002x).

Epidemiologic Studies of Exposure to Insecticides

Several studies examined the relationship between exposure to specific insecticides, classes of insecticides, and insecticides in general and the risk of adult leukemia. The discussion below describes the key studies evaluated by the committee in making its conclusion of associaiton, and results of these studies are found in Table 5.12.

Of the studies that examined the relationship between exposure to insecticides and the risk of adult leukemia, only one evaluated the role of specific insecticides—a case–control study by Brown and colleagues (1990) of confirmed leukemias in 578 men in Minnesota (1980–1982) and Iowa (1981–1983). The authors interviewed cases or close relatives to determine exposures and the use of 112 pesticides, including 58 insecticides. Risk of leukemia with ever handling specific animal insecticides was evaluated for carbaryl (OR = 1.3, 95% CI = 0.5–3.2), dichlorvos (OR = 2.0, 95% CI = 1.2–3.5), lindane (OR = 1.1, 95% CI = 0.7–1.7), and malathion (OR = 1.2, 95% CI = 0.8–2.0). Risk of leukemia with ever handling crop insecticides was evaluated for carbaryl (OR = 0.9, 95% CI = 0.4–2.1), diazinon (OR = 1.2, 95% CI = 0.6–2.1), lindane (OR = 1.6, 95% CI = 0.8–3.2), and malathion (OR = 0.9, 95% CI = 0.4–1.9). The authors also conducted supplemental interviews of self-identified Iowa pesticide users to obtain information about the usual number of days per year that insecticides were handled. No clear exposure–response patterns were found between leukemia risk and increasing number of days per year of insecticide use.The study authors acknowledge the role of nondifferential exposure misclassification (including difficulty in recalling information by self-respondents and next of kin) and recall bias in the findings and note that the multiple statistical comparisons make it likely that some findings may be due to chance alone. Uncontrolled confounding by exposure to other insecticides or pesticides, such as herbicides, is also a limitation of the study.

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A case–control study by Clavel and colleagues (1996) examined HCL and exposure to various classes of insecticides, including organophosphorous insecticides, carbamates, and pyrethrins. The investigators included 226 histologically confirmed cases of HCL in hospitals in France in 1980–1990 and 425 hospital-based controls hospitalized in the same hospitals at about the same time as the cases. Patients admitted for cancer or for work-related diseases or accidents were not eligible to serve as controls. All cases and controls were sent self-administered questionnaires to ascertain occupational and leisure time exposures, sociodemographic characteristics, smoking, and other behaviors. All persons who identified themselves as farmers were interviewed at home by occupational physicians who specialized in agricultural work. Among farmers, risk of HCL was increased with exposure to organophosphorous insecticides (OR = 2.6, 95% CI = 1.1–5.7) and pyrethrins (OR = 1.6, 95% CI = 0.7–3.9) but not carbamates (OR = 0.7, 95% CI = 0.2–2.8). Limitations of the study include the potential for nondifferential misclassification due to recall difficulties and the grouping of insecticides into broad categories. Because data on exposure to the classes of insecticides were missing for more than 50% of the self-identified farmers, results were interpreted cautiously.

The case–control study by Brown and colleagues (1990) described above found an increased risk of all leukemias with ever handling pyrethrins (OR_{animal} = 3.7, 95% CI = 1.3–10.6), carbamates (OR_{animal} = 1.5, 95% CI = 0.6–3.6; OR_{crops} = 1.4, 95% CI = 0.9–2.2) and organophosphorous insecticides (OR_{animal} = 1.5, 95% CI = 1.0–2.1; OR_{crops} = 1.2, 95% 0.8–1.8).

Nanni and colleagues (1996) conducted a population-based case–control study in agricultural areas in Italy to examine the relationship between CLL and NHL and exposure to insecticides, which was discussed earlier in this chapter. The odds ratios for all CLL and low-grade NHL cases were elevated for exposure to carbamates based on recall data (OR = 3.08, 95% CI = 1.05–9.00) and the matrix (OR = 2.95, 95% CI = 1.01–8.60). The odds ratios were also increased for exposure to insecticides based on both recall data and the matrix, but only the odds ratio based on recall was statistically precise. Since the study combined cases of CLL and low-grade NHL in its analysis, the study's findings are limited and the true effect of exposure on CLL cannot be determined and the results are not captured in Table 5.12.

Two of the studies described above examined the association between leukemia and exposure to insecticides in general. Brown and colleagues found an increase in CLL with use of any insecticide (OR = 1.3, 95% CI = 1.0–1.8), as well as increases with overall animal or crop use. An increased HCL risk with exposure to insecticides in general was reported by Clavel and colleagues (OR = 1.8, 95% CI = 1.1–3.0) (1996).

Nordstrom and colleagues (1998) conducted a population–based case–control study of 121 men with HCL identified from the Swedish Cancer Registry and diagnosed in 1987–1992 and 484 matched controls. Study participants completed mailed questionnaires, and a trained interviewer followed up by telephone with supplementary questions. Although an association was found when adjusting for age only, (OR = 2.0, 95% CI = 1.1–3.5), controlling for other variables not explicitly stated eliminated any association (OR = 0.7, 95% CI = 0.3–1.7).

Richardson and colleagues (1992) reported on a case–control study of confirmed acute leukemia cases and hospital-based controls (not leukemia or lymphoma) identified in departments other than the department from which the cases were selected (hematology).

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Exposure to insecticides was determined through interviews of the cases and controls and independently assessed by an industrial hygienist. Risk of acute leukemia was increased with exposure to insecticide (OR = 1.7, 95% CI = 1.0–3.1); the magnitude of the risk increased with 10 years or more of exposure (OR = 4.0, 95% CI = 1.2–13.2). The authors also examined the relationship between exposure to insecticides and the two cytologic types of acute leukemia—ALL and AML. Both increased with exposure to insecticides (OR_{ALL} = 3.29, 95% CI = 1.16–9.36; OR_{AML} = 1.51, 95% CI = 0.79–2.89).

Only one case of leukemia was observed in the study of male chemical workers (Rapiti et al., 1997). Semenciw and co-workers (1994) assembled a cohort of 155,547 farmers from the population of Alberta, Saskatchewan, and Manitoba, Canada, by linking the 1971 Canadian Censuses of Agriculture and Population. Diagnosis of leukemia was determined from death certificates filed in 1971–1987 and linked to the cohort. Exposure was considered to be the number of acres sprayed with insecticides in 1970; risk of leukemia was not increased by spraying of 90 acres or more with insecticides (RR = 1.08, 95% CI = 0.51–2.28) on the basis of seven cases. Extremely small numbers and lack of individual exposure data limit the value of the findings of both studies.

Two studies identified leukemia cases and usual occupation as farmers from death certificates (Blair and Thomas, 1979; Burmeister et al., 1982); insecticide exposure was estimated from quantity of use in the county of usual residence. The studies are of little value for supporting conclusions because neither leukemia diagnosis nor the agents were verified, and both are probably subject to nondifferential misclassification, which would tend to move associations toward the null value.

A few studies already discussed above (Clavel et al., 1996; Richardson et al., 1992) and others (Ciccone et al., 1993; Johnson et al., 1993; Kristensen et al., 1996; Pasqualetti et al., 1991; Viel and Richardson, 1993; Zhong and Rafnsson, 1996) examined the relationship between exposure to pesticides and adult leukemia among various, occupationally exposed populations, but do not provide exposure specificity beyond the broad grouping of pesticides. In addition, studies of pesticide applicators (Cantor and Booze, 1991; Fleming et al., 1999a,b; Sperati et al., 1999), farmers (Brownson et al., 1989; Rafnsson and Gunnarsdottir, 1989), and agricultural workers (Hansen et al., 1992; Linet et al., 1994) use job titles as surrogates for exposure. As a result, the lack of specific and validated exposure measurements limits the contributions of these studies toward determining an association between exposure to insecticides under review and leukemia risk.

Summary and Conclusion

Although specific and accurate exposure information on insecticide use is difficult to ascertain in epidemiologic studies, most populations studied involve workers who use insecticides on a regular basis over the course of many years. A majority of the studies discussed above reported an increased risk of leukemia, especially among those exposed to organophosphorous insecticides. The studies on specific organophosphorous agents, such as diazinon, dichlorvos, and malathion, as well as on the broader category of insecticides provided additional support to a conclusion on exposure to organophosphorous compounds. Most of the findings were of sufficient statistical power to detect a precise estimate of risk. Given that most studies included all types of leukemia and that more specific cell types were identified in only a limited number of studies, the committee focused its conclusion on adult leukemia broadly. Table 5.12 provides a description of the population, the number of

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exposed cases, the estimated risk, and the confidence interval for the studies reviewed by the committee in making its conclusion regarding association.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to organophosphorous insecticides and adult leukemia.

TABLE 5.12 Selected Epidemiologic Studies—Adult Leukemia and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific Insecticides			
Case–Control Studies			
Brown et al., 1990	Residents of Iowa and Minnesota[a]		
	Carbaryl		
	Animal insecticide, ever handled	7	1.3 (0.5–3.2)
	Animal insecticide, 20 years ago	4	3.0 (0.7–12.4)
	Crop insecticide, ever handled	9	0.9 (0.4–2.1)
	Diazinon		
	Crop insecticide, ever handled	17	1.2 (0.6–2.1)
	Crop insecticide, 1–4 days/year	8	2.1 (0.8–5.6)
	Crop insecticide, 5–9 days/year	2	0.5 (0.1–2.4)
	Crop insecticide, 10+ days/year	0	—
	Dichlorvos		
	Animal insecticide, ever handled	26	2.0 (1.2–3.5)
	Animal insecticide, 1–4 days/year	5	1.3 (0.4–4.0)
	Animal insecticide, 5–9 days/year	0	—
	Animal insecticide, 10+ days/year	5	3.8 (1.0–14.8)
	Lindane		
	Animal insecticide, ever handled	38	1.1 (0.7–1.7)
	Animal insecticide, 20 years ago	28	1.4 (0.8–2.3)
	Animal insecticide, 1–4 days/year	15	1.1 (0.5–2.0)
	Animal insecticide, 5–9 days/year	3	1.1 (0.3–4.1)
	Animal insecticide, 10+ days/year	10	1.6 (0.7–3.7)
	Crop insecticide, ever handled	14	1.6 (0.8–3.2)
	Crop insecticide, 1–4 days/year	6	3.5 (0.9–12.6)
	Crop insecticide, 5–9 days/year	2	1.2 (0.2–6.9)
	Crop insecticide, 10+ days/year	3	1.3 (0.3–5.3)
	Malathion		
	Animal insecticide, ever handled	30	1.2 (0.8–2.0)
	Animal insecticide, 20 years ago	15	1.5 (0.8–2.9)
	Animal insecticide, 1–4 days/year	5	0.5 (0.1–1.3)
	Animal insecticide, 5–9 days/year	0	—
	Animal insecticide, 10+days/year	7	3.2 (1.0–10.0)
	Crop insecticide, ever handled	10	0.9 (0.4–1.9)
	Crop insecticide, 1–4 days/year	4	1.2 (0.3–3.9)
	Crop insecticide, 5–9 days/year	2	0.8 (0.2–4.4)
	Crop insecticide, 10+ days/year	0	—
	Pyrethrins		
	Animal insecticide, ever handled	8	3.7 (1.3–10.6)
	Animal insecticide, 20 years ago	5	3.8 (1.0–14.8)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Studies			
Clavel et al., 1996	HCL cases in France		
	Organophosphorous agents	14	2.6 (1.1–5.7)
	Pyrethrins	10	1.6 (0.7–3.9)
	Carbamates	3	0.7 (0.2–2.8)
Brown et al., 1990	Residents of Iowa and Minnesota		
	Carbamates (animal insecticide)	8	1.5 (0.6–3.6)
	Carbamates (crop insecticide)	44	1.4 (0.9–2.2)
	Organophosphorous agents (animal	55	1.5 (1.0–2.1)
	insecticide)	51	1.2 (0.8–1.8)
	Organophosphorous agents (crop insecticide)		
Insecticides			
Cohort Studies—Mortality			
Rapiti et al., 1997	Chemical workers in Italy	1	2.00 (0.10–9.49)
Semenciw et al., 1994	Canadian farmers who sprayed 90+ acres	7	1.08 (0.51–2.28
Case–Control Studies			
Clavel et al., 1996	HCL cases in France	37	1.8 (1.1–3.0)
Nordstrom et al., 1998	HCL cases in Sweden		
	Univariate analysis	22	2.0 (1.1–3.5)
	Multivariate analysis	22	0.7 (0.3–1.7)
Richardson et al., 1992	Residents near Paris, France		
	Insecticides	22	1.7 (1.0–3.1)
	≤10 years	1	0.5 (0.1–4.1)
	>10 years	7	4.0 (1.2–13.2)
	Insecticides and ALL	6	3.29 (1.16–9.36)
	Insecticides and AML	16	1.51 (0.79–2.89)
Brown et al., 1990	Residents of Iowa and Minnesota		
	Used any insecticide (all types)	250	1.1 (0.9–1.3)
	Animal insecticide (all types)	238	1.1 (0.8–1.3)
	Crop insecticide (all types)	134	1.1 (0.8–1.4)
	CLL (any insecticide)	122	1.3 (1.0–1.8)

[a]For all data points, risk estimates for specific animal and crop insecticides are taken from analysis of ever having handled these insecticides.

CHILDHOOD CANCER

Childhood cancer is defined by ACS as cancer diagnosed between birth and the age of 14 years. The causes of most childhood cancers are not well known, especially with regard to potential environmental risk factors. Some of the suggested risk factors are genetics, advanced maternal age, birthweight of more than 4000 g, prenatal viral exposure, prenatal radiation exposure, parental cigarette smoking, and parental occupation (Ross and Swensen, 2000).

Childhood cancers are rare. Developments in treatment and supportive care for some types have enabled 75% of afflicted children to survive 5 years or more, and mortality from all childhood cancers combined has declined by 50% since 1973. Nevertheless, cancer is still the leading cause of death from disease in children age up to 14 years old (ACS, 1999).

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Leukemia is the most common cancer in children and accounts for almost one-third of all childhood cancers. ALL is the most common leukemia in children, accounting for nearly 75% of all leukemia cases (ACS, 2002k). Slightly more prevalent among white children and among boys, ALL generally occurs in early childhood, particularly at the age of 2–3 years. The 5-year survival rate for ALL among children has increased to nearly 80%, primarily because of advances in treatment (ACS, 2002k).

Most of the remaining childhood leukemia cases are categorized as AML, which occurs most often in the first 2 years of life and is less common among older children. However, the incidence of AML increases during the teenage years to adult rates. Developments in treatment have improved the survival rate for children with AML, which has a 5-year survival rate of about 40% (ACS, 2002k).

Prenatal exposure to radiation is known to be associated with the development of ALL. Some genetic disorders—such as Li-Fraumeni syndrome, Down syndrome, and Klinefelter syndrome—also are associated with ALL, and chemotherapeutic agents are associated with secondary leukemias later in childhood or in adulthood. Paternal occupational exposure to chemicals and solvents, radiation, and chemical contamination of ground water have also been hypothesized to be associated with childhood leukemia (ACS, 2002k).

CNS cancers include malignant brain and spinal cord tumors. Brain tumors are the second most common group of cancers affecting children, accounting for about 20% of all childhood cancers. Common types of childhood brain tumors include astrocytomas (tumors originating in the brain cells), primitive neuroectodermal tumors (PNETs) (tumors that develop from primitive stem cells), and germ cell tumors. Neuroblastoma, a type of CNS tumor derived from embryonic neural crest cells, is the third most common form of cancer in children and accounts for 7–10% of all childhood cancers. Neuroblastoma is the most common cancer in children under 1 year old, accounting for 50% of all cancers in infants (ACS, 2002l).

The etiology of childhood brain cancer appears to be multifactorial, with no clear primary cause. Such genetic syndromes as Li-Fraumeni syndrome and von Recklinghausen's disease are known to be associated with a modest fraction of these tumors, and it is suspected that other risk factors are also involved. One well-established risk factor for the development of brain tumors is exposure to ionizing radiation, which occurs during the treatment of other cancers. Other factors—such as exposure to nitrates, aspartame, and electromagnetic fields—have been studied, but no conclusive evidence clearly implicates them as causal factors. More than 50% of children with brain tumors (all types combined) survive over 5 years (ACS, 2002l).

Lymphomas have two major categories based on cell histology: HD and NHL, both of which are relatively rare in children, but which together are the third most common cancer in children. Representing about 4% of all childhood cancers, NHL occurs about 1½ times as often as HD in children. NHL is 3 times more common in boys than in girls and twice as common in white children as in black children; its incidence peaks at the age of 7–11 years. Little is known about the etiology of childhood NHL. Known risk factors include genetic diseases that cause abnormal or deficient immune system development and radiation exposure (usually during the course of cancer therapy). The 5-year survival rate of children diagnosed with NHL in its early stages is more than 90% (ACS, 2002m).

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Epidemiologic Studies of Exposure to Insecticides

Most of the studies on childhood cancers are case–control that use cancer registries with well-characterized, pathologically confirmed diagnoses as a basis for selection of cases. However, exposure assessment generally relies on questionnaires or interviews with parents to recall exposures to various agents before, during, or after birth. As a result, the specificity of the agents and the actual period of exposure are subject to recall and misclassification bias.

In making conclusions of association on childhood cancers and other reproductive outcomes (Chapter 8), the committee focused on studies that examine the agents of concern during preconception rather than during or after gestation. That approach was taken to make the conclusions as relevant as possible to Gulf War veterans. It is the committee's understanding that if a pregnancy occurred during the Gulf War, the pregnant woman would have been removed from the Persian Gulf (Neish and Carter, 1991). However, if evidence to the contrary becomes available, future Gulf War studies will consider studies of gestational exposures.

It should be noted that the majority of childhood cancer studies focus on exposure to agents during pregnancy. The committee discusses several of those studies below and indicates whether they also assessed preconception exposure. If they did not, they were not considered primary evidence in making conclusions of association.

Childhood Leukemia

Only a few studies have elicited information about specific insecticides or classes of insecticides and the risk of developing childhood leukemia. A number of studies examined exposure to pesticides in general, but they were not useful for drawing conclusions for the purposes of this review as they lacked specific information on the types of pesticides used. The following discussion describes the key studies that led to the committee's conclusion.

Leiss and Savitz (1995) studied all cases of leukemia among 252 in children 0–14 years old diagnosed with cancer in Denver in 1976–1983 and compared them with community controls (n = 222). The three exposure periods assessed were 3 months before birth to birth, birth to 2 years before diagnosis, and 2 years before diagnosis to diagnosis. No risk of childhood leukemia was found for cases whose homes underwent insect extermination during the last 3 months of pregnancy (OR = 0.4, 95% CI = 0.1–1.2, based on four cases) whereas a positive relationship was observed for yard treatment (OR = 1.1, 95% CI = 0.6–1.9) and the use of pest strips (OR =3.0, 95% CI = 1.6–5.7) for the same exposure period. The study authors identified diazinon, chlorpyrifos, and other pesticides as the ingredients most likely to be used in home extermination, and the herbicide 2,4-D, carbaryl, diazinon, and others as most likely ingredients used in yard treatments. Pest strips contain the active ingredient dichlorvos. The study found an increased risk of childhood leukemia in children whose mothers used pest strips during the last 3 months of pregnancy. Limitations acknowledged by the authors include the crude measures of exposure, non-response (about 29% of cases and 21% of controls), and the method of control selection. In addition, the study did not consider exposure during preconception, the time period of interest for this report.

Infante-Rivard and colleagues (1999) studied 491 children, 0–9 years old, with ALL diagnosed in 1980–1993 in Quebec, Canada. Cases were identified on the basis of a clinical

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diagnosis by an oncologist or hematologist in a tertiary care center. Population-based controls were matched one-to-one on age, sex, and region of residence at the time of diagnosis. Exposure information on home use of pesticides and insecticides was assessed with telephone interviews based on a standardized questionnaire. The mother and father of each case and control were interviewed separately, but the questions regarding pesticide and insecticide exposure were directed only at the mothers. The study provided an analysis of two exposure periods: 1 month before conception to the end of pregnancy and during childhood. The analysis did not report separately on the 1 month before conception. When the mothers were asked about insecticide use during pregnancy in the home by specific type of insect, the ORs ranged from 1.37 for insecticides used against mites and spiders (95% CI = 0.73–2.58) to 2.47 for moths (95% CI = 1.43–4.28). Use of plant insecticides also showed an increased risk of ALL (OR = 1.97, 95% CI = 1.32–2.94), whereas use of repellents and sprays for outdoor insects revealed no risk (OR = 0.70, 95% CI = 0.45–1.09). The risk of childhood ALL showed an exposure–response relationship for increasing use of plant insecticides during pregnancy, although the higher frequency category was based on a small number of exposed cases: $OR_{1\text{-}5\ times} = 1.89$ (95% CI = 1.20–2.97) based on 60 exposed cases, and $OR_{more\ than\ 5\ times} = 4.01$ (95% CI = 1.12–14.32) based on three cases. One limitation of this study is the lack of information on the specific insecticides used to control or eliminate the pests identified in and around the home. The authors do, however, suggest that chlorpyrifos, diazinon, dichlorvos, malathion, and carbaryl are likely to have been used indoors and around the home by the mothers interviewed. For the purpose of this report, another limitation is the lack of analysis on preconception exposures.

For the same 491 cases of childhood ALL, Infante-Rivard and Sinnett (1999) reported on paternal occupational exposures to insecticides that occurred before conception only. Exposures were coded by industrial hygienists on the basis of occupational job titles and industry type. For children of fathers exposed to insecticides in the workplace before conceiving a child, an increased risk of ALL was found (OR = 1.38, 95% CI = 0.87–2.18). An increased risk was also observed for exposure to pesticides in general, which included insecticides, herbicides, rodenticides, fungicides, molluscicides, and nematodicides. In this study, there was a possibility of confounding by various types of pesticides. Given that the odds ratio for insecticides was lower than for pesticides in general, one cannot rule out the possibility of confounding by exposure to another class of pesticides.

Several studies examined childhood leukemia with broader measures of exposure to pesticides. Although informative, those studies do not provide separate data on exposure to insecticides. Buckley and colleagues (1989) reported an increased risk of acute non-lymphocytic leukemia (ANLL) with maternal or paternal occupational exposure to pesticides before pregnancy (paternal exposure OR = 1.7; maternal exposure OR = 3.0, $0.05 < p < 0.10$), as did Meinert and colleagues (1996, 2000) for childhood leukemia and paternal or maternal occupational exposure to insecticides, herbicides, or fungicides in the year before pregnancy and during pregnancy. Two other studies of exposure to pesticides during pregnancy found increased risks of childhood leukemia (Lowengart et al., 1987; Shu et al., 1988).

Childhood Brain and Other Central Nervous System Tumors and Lymphomas

The committee reviewed the available literature on exposure to insecticides and the risk of brain and other nervous system tumors, including neuroblastoma, astrocytic glioma,

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primitive PNET, malignant germ-cell tumors, and lymphoma (such as NHL). The literature on other childhood cancers (such as Wilms' tumor and Ewing's bone sarcoma) did not examine the insecticides under review.

Few studies have attempted to evaluate the relationship between parental exposure to insecticides before conception and the risk of other childhood cancers. The following discussion highlights the issues of concern and the key studies reviewed by the committee in making its conclusion.

No studies addressed exposure to specific insecticides only before conception in relation to childhood cancers other than leukemia. Davis and colleagues (1993) reported on a study of 45 children 0–10 years old with brain cancer diagnosed in 1985–1989. They found a higher risk in children whose mothers used No-Pest-Strips (containing dichlorvos) during pregnancy than in friend controls (OR = 5.2, 95% CI = 1.2–22.2, based on eight cases) or cancer controls (OR = 1.9, 95% CI = 0.6–5.9). When the mothers used carbaryl, diazinon, or any insecticide in the garden or orchard, an increased risk of childhood brain tumors was found in comparison to friend and cancer controls. When the mothers reported using pesticides on pets and being directly exposed to the agents, a lower risk of childhood brain tumors was found than in friend and cancer controls. However, the study did not assess preconception exposures.

In the study discussed above, Leiss and Savitz (1995) compared all cases of brain tumors among 252 children 0–14 years old diagnosed with cancer in Denver in 1976–1983 with community controls (n = 222). An increased risk of brain tumors was found in cases whose homes underwent insect extermination during the last 3 months of pregnancy (OR = 1.3, 95% CI = 0.7–2.1) or used pest strips (OR = 1.5, 95% CI = 0.9–2.4), whereas no relationship was observed for yard treatment (OR = 0.6, 95% CI = 0.3–1.1). The authors also found an increased, but imprecise, risk of childhood lymphoma in cases whose homes underwent extermination during the last 3 months of pregnancy (OR = 1.2, 95% CI = 0.4–3.9) or used pest strips (OR = 1.4, 95% CI = 0.7–2.5). No risk was observed in cases whose yards were treated with herbicides and insecticides during pregnancy (OR = 0.5). There were no separate analyses for preconception exposures.

Daniels and colleagues (2001) conducted a case–control study of neuroblastoma in children diagnosed in 1992–1994 and identified through the Children's Cancer Study Group and the Pediatric Oncology Group, collaborative clinical trial groups in the United States and Canada. The groups confirmed the diagnosis of the 538 cases in children 0–5 years old at the time of diagnosis. Mothers of cases and controls provided information on parental job histories, occupational exposure, residential use of insecticides, and other factors; fathers were asked to participate only if the mothers completed the interviews. Parents were interviewed separately about exposures that occurred 1 month before conception to the date of diagnosis. The authors stated that the pesticides used in the home by parents and professional exterminators were mostly insecticides. When both parents reported having professional insect extermination in the home 1 month before or during pregnancy, no risk of neuroblastoma was found (OR = 1.0, 95% CI = 0.5–2.1). An increased risk was observed when both parents reported using pesticides at home (OR = 1.3, 95% CI = 0.8–3.3). Most parents in the study were asked to recall exposures over periods that occurred 1–5 years earlier. As a result, although the large sample and confirmation of exposure by both parents separately are strengths, it is difficult to say whether the small association indicates or

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reflects imprecise exposure measurement. The study did not provide a separate analysis of preconception exposures.

Histologically confirmed cases of neuroblastoma in children 0–14 years old and diagnosed were included in a case–control study conducted by Kerr and colleagues (2000). The 372 controls were matched by year of birth to the 183 cases diagnosed in New York state (excluding New York City) between 1976 and 1987. The mothers provided data on parental occupations held during pregnancy. An increased risk of neuroblastoma was observed among children whose mothers reported exposure to insecticides during pregnancy (OR = 2.3, 95% CI = 1.4–3.7) and whose fathers reported the same exposure (OR = 1.7, 95% CI = 1.0–2.7). Limitations acknowledged by the authors include potential misclassification due to job-coding errors, the large number of multiple comparisons, interviewer bias, self-reported exposure (of both mothers and fathers) by mothers, and recall bias. Additionally, information regarding occupation prior to conception was not collected..

Pogoda and Preston-Martin (1997) reported a case–control study of childhood brain tumors diagnosed in 1984–1991 in Los Angeles County, California, in children up to 19 years old at diagnosis. Mothers of the 224 cases and 218 controls were interviewed regarding childhood exposure to insecticides and prenatal parental exposure. An OR of 1.3 (95% CI = 0.7–2.4) was found between prenatal exposure to insecticides and the risk of pediatric brain tumors on the basis of 26 exposed cases. An increased risk was also observed for prenatal use of flea and tick products (OR = 1.7, 95% CI = 1.1–2.6) on the basis of 76 exposed cases. However, preconception exposure was not assessed separately, and the case series included subjects older than those in most other childhood cancer studies.

Bunin and colleagues (1994) conducted a case–control study of children with astrocytic glioma and PNET and maternal exposure to insect sprays or pesticides during pregnancy. An increased risk of astrocytoma was observed if mothers used insect sprays or other pesticides at some point during pregnancy (OR = 1.5, 95% CI = 0.8–2.7), but there was not an increased risk of PNET (OR = 0.7, 95% CI = 0.4–1.4); furthermore, if mothers used such pesticides weekly during their pregnancy, an increased risk was observed for astrocytoma but not for PNET (OR = 2.2 and 1.0, respectively). No information was available on preconception exposure.

Malignant germ-cell tumors (MGCTs) are rare childhood brain cancers derived from primordial germ cells. Shu and colleagues (1995) conducted an exploratory case–control study of 105 cases of MGCT identified through the Children's Cancer Study Group and 639 community controls identified through random-digit dialing and matched by age. The cases were diagnosed in 1982–1989 and were less than 15 years old at the time of diagnosis. Parents of cases were asked to complete a 22-page self-administered questionnaire regarding occupational and home exposure that occurred during the preconception, prenatal, and postnatal periods. When the three periods of exposure were combined, an increased risk of MGCT was observed for reported maternal and paternal exposure to insecticides or herbicides (OR = 2.4, 95% CI = 0.9–6.9 for mothers; OR = 1.8, 95% CI = 0.7–5.0 for fathers). However, the lack of data on timing of exposure with respect to pregnancy limits the usefulness of the data for the committee's purposes, as does the fact that exposure to insecticides and herbicides are combined. Although an increased risk was reported for domestic exposure to insecticides or herbicides before, during, and after pregnancy, the authors did not report the results for those exposure intervals separately, because the estimates were less stable.

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In 2000, Buckley and colleagues reported on a case–control study of cases of NHL and leukemia identified through the Children's Cancer Study Group. Increased risks of childhood NHL were observed: if mothers used household insecticides 1–2 days per week (OR = 2.62) or on most days (OR = 7.33) during pregnancy; if mothers reported having professional insect treatments around the home (OR = 2.98, 95% CI = 1.44–6.16) at the time of pregnancy; or if either parent reported being exposed to pesticides occupationally (OR = 1.74, 95% CI = 0.82–3.69). Exposure one month prior to conception was assessed, but not analyzed separately. Paternal exposure was not considered.

Several studies examined the relationship between exposure to pesticides in general—including insecticides, herbicides, fungicides, and other types of pest agents—and the risk of some childhood cancers, including brain and other CNS cancers and lymphomas. However, the role of insecticides cannot be differentiated from that of herbicides, fungicides, or other pesticides in assessing the risk of childhood cancers. A majority of the studies reviewed show an increased risk of childhood cancers with exposure to pesticides before or during pregnancy. Studies on pesticide exposure include those by Cordier and colleagues (1994), Feychting and colleagues (2001), Holly and colleagues (1998), and McCredie and colleagues (1994) for brain and other nervous system tumors; and Meinert and colleagues (2000) for NHL.

Summary and Conclusion

The studies of exposure to insecticides and childhood cancers have focused primarily on maternal exposure during pregnancy. Only one study examined the relationship between paternal exposure to insecticides before conception and childhood leukemia (Infante-Rivard et al., 1999). Other studies combined exposures prior to and during pregnancy. Tables 5.13 and 5.14 summarize the results of the most relevant studies reviewed by the committee in assessing exposure to insecticides and the risk of childhood cancers, specifically childhood leukemia, brain and other nervous system tumors, and lymphomas.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between paternal or maternal preconception exposure to the insecticides under review and certain childhood cancers, including childhood leukemia, brain and other central nervous system cancers, and non-Hodgkin's lymphoma.

TABLE 5.13 Selected Epidemiologic Studies—Childhood Leukemia and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Insecticides			
Case–Control Studies			
Infante-Rivard et al., 1999	ALL cases in Quebec, Canada		
	Maternal domestic exposure 1 month before pregnancy to end of pregnancy		
	Cockroaches, ants, flies, bees, wasps	168	1.79 (1.34–2.40)
	Moths	45	2.47 (1.43–4.28)
	Mites and spiders	23	1.37 (0.73–2.58)
	Insects	96	1.59 (1.11–2.26)
	Termites	8	1.89 (0.56–6.37)
	Plant insecticides	78	1.97 (1.32–2.94)
	Repellents and sprays for outdoor insects	46	0.70 (0.45–1.09)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Infante-Rivard and Sinnett, 1999	ALL cases in Quebec, Canada Paternal preconception occupational exposure Insecticides	50	1.38 (0.87–2.18)

TABLE 5.14 Selected Epidemiologic Studies—Other Childhood Cancers and Exposure to Insecticides

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Brain and Other Nervous System Tumors			
Case–Control Studies			
Daniels et al., 2001	Neuroblastoma (Children's Study Group)		
	Parental exposure 1 month before conception through pregnancy		
	Extermination in home	23	1.0 (0.5–2.1)
	Home insecticide use	93	1.3 (0.8–3.3)
Shu et al., 1995	Malignant germ-cell tumors (Children's Study Group)		
	Exposure before, during, and after diagnosis (combined)		
	Insecticides or herbicide (maternal)	7	2.4 (0.9–6.9)
	Insecticides or herbicides (paternal)	7	1.8 (0.7–5.0)
Non-Hodgkin's Lymphoma			
Case–Control Study			
Buckley et al., 2000	Childhood NHL (Children's Study Group)		
	Maternal exposure 1 month before pregnancy, during pregnancy, or while nursing (combined)		
	Personal use of insecticides (1–2 days/week)	17	2.62 (0.96–7.18)
	Personal use of insecticides (most days)	6	7.33 (0.84–63.85)
	Professional insecticide extermination	31	2.98 (1.44–6.16)

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6

CANCER AND EXPOSURE TO SOLVENTS

INTRODUCTION

The associations between exposure to organic solvents and the incidence of and mortality from cancer have been investigated extensively in a number of industries and occupations, including dry-cleaning, painting, printing, and rubber and shoe manufacturing. As a result, the body of evidence on exposure to organic solvents and cancer reviewed by the committee is quite large compared with that on other health effects. To help the reader become more familiar with the studies on exposure to solvents and cancer, this chapter is organized differently from Chapter 5.

Following this general introduction is a description of the major occupational cohort studies that are cited throughout the chapter; these studies provide findings for multiple cancer outcomes. The committee describes the essential study design characteristics and pertinent information for each of these cohorts organized by the type of solvent exposure.

The occupational cohort studies examined populations with known or suspected exposure to the solvents under review. Many of them have been updated and expanded to include more cohort members, longer periods of assessment, and other estimates of exposure. All of the various studies that follow a particular cohort, such as the NIOSH Pliofilm cohort, are described together in Table 6.1. The committee reviewed all the papers related to each major cohort in drawing its conclusions of association, but it is usually the findings from the most recent papers that are provided in the data-analysis tables at the end of the section on each cancer site. In some cases, results from the earlier papers were never reproduced, so the committee used the earlier results in its analysis.

A description of key case–control studies at the beginning of each section is followed by a table that outlines the studies' characteristics and design elements and is similar to the table of cohort studies at the beginning of the chapter. Discussions of strengths and limitations of the studies that formed the basis of the committee's conclusions are presented in the sections on the specific outcomes.

Background information on the types of cancer or cancer in general is provided in Chapter 5, and the reader is referred to those sections for that information. A review of the pertinent toxicology and findings from other organizations charged with evaluating the carcinogenicity of organic solvents is provided at the end of this introduction.

As in Chapter 5, the cancer outcomes are presented in the order of the ninth revision of the *International Classification of Disease* (ICD-9).

The Literature on Exposure to Organic Solvents

The literature on exposure to organic solvents and cancer outcomes provides information on specific solvent exposures (for example, benzene, trichloroethylene, and

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tetrachloroethylene), on mixtures of specific organic solvents, or on mixtures of unspecified solvents. In many studies, exposure to solvents was not assessed specifically; rather, surrogates of exposure were used, such as job title, industry type, or occupation.

As is discussed in Chapter 2, a study's ability to determine exposure accurately and specifically is critical in evaluating its overall quality. For the purposes of this report, the committee used studies that assessed exposure to specific organic solvents or to solvent mixtures as the primary evidence for its conclusions. The committee also included surrogates of exposure in drawing its conclusions, but it viewed those studies as supportive or supplemental evidence. Those studies included exposure of painters, printers, aircraft maintenance and manufacturing workers, service-station attendants, and shoe and boot manufacturers. All those studies are included in the data-analysis tables that accompany discussions of each cancer outcome.

The committee found most of the cancer literature focused on the following compounds: benzene, trichloroethylene, tetrachloroethylene, methylene chloride, and mixtures of unspecified organic solvents. Therefore, most of the committee's conclusions on cancer outcomes are focused on exposure to those compounds. A smaller number of studies analyzed associations between cancer outcomes and toluene, xylene, isopropyl alcohol, methyl ethyl ketone, phenol, and other individual solvents, but for most agents, there was insufficient evidence for the committee to draw conclusions.

For exposure to tetrachloroethylene, the committee included studies of dry-cleaning and laundry workers as part of the primary evidence in drawing conclusions of associations. As a result, the conclusions related to exposure to tetrachloroethylene are also related to exposure to "dry-cleaning solvents." The committee acknowledges that dry cleaners and launderers are likely exposed to other organic solvents and chemicals, including naphtha, Stoddard solvent, carbon tetrachloride, trichloroethylene, and 1,1,1-trichloroethane (IARC, 1995). As a result, the committee decided to consider studies of both tetrachloroethylene and dry-cleaning solvents in forming their conclusions, thereby including the possibility that one of the other solvents used in that industry contributed to the risks observed in some of the studies on dry cleaners and launderers.

The committee based its review of cancer outcomes only on studies of humans that had a comparison or control group (cohort and case–control studies). Case reports, case series, review articles, and meta-analyses related to cancer were excluded from the committee's review. Although the committee reviewed ecologic, cross-sectional, proportionate mortality ratio (PMR), and mortality odds ratio studies, it did not consider them critical to its decision and excluded them from the discussions. Chapter 2 describes their specific limitations.

Toxicity and Determination of Carcinogenicity

Excess incidence of cancer has been observed in animals exposed to the specific organic solvents reviewed by the committee. Benzene, perhaps the most thoroughly investigated solvent, is a well-established carcinogen and has repeatedly been shown to induce hematopoietic cancers and cancers of the ovaries, mammary glands, pancreas, and liver (ATSDR, 1997a). The International Agency for Research on Cancer (IARC) has determined that benzene is "carcinogenic to humans" as determined in studies of both humans and animals. IARC bases its determination of benzene's carcinogenicity on evidence from human studies that is considered "sufficient," whereas the available animal

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data are considered "limited." Most of the human studies cited by IARC involve the increased risk of leukemia and other lymphatic and hematopoietic cancers (IARC, 1987). The National Toxicology Program (NTP) has also classified benzene as "known to be a human carcinogen" in its most recent report on carcinogens on the basis of animal and human studies (NTP, 2001).

On the basis of animal studies, trichloroethylene has been associated with liver cancer in one strain of one species (mouse) (ATSDR, 1997b). Liver and renal cell cancers and mononuclear cell leukemia have typically been seen after exposure to tetrachloroethylene. According to the Agency for Toxic Substance and Disease Registry (ATSDR, 1997c), the relevance to humans of rodent toxicology studies on trichloroethylene and tetrachloroethylene is unclear, given that some mechanisms of action differ. However, a great deal of research has been conducted over the last decade, and some mechanisms of action appear to be similar in rodents and humans such as genotoxic and cytotoxic actions of mercapturic acid derivatives of both trichloroethylene and tetrachloroethylene in the kidney (see Chapter 4 for more information). IARC has also reviewed trichloroethylene and tetrachloroethylene and determined that both are "probably carcinogenic to humans." The evidence from animal studies is stronger and considered to be "sufficient," whereas the evidence from human studies is considered "limited" (IARC, 1995). In addition, the NTP has identified both trichloroethylene and tetrachloroethylene as "reasonably anticipated to be human carcinogens" (NTP, 2001).

Exposure to methylene chloride in some rodent species has consistently produced excess numbers of cancers of the liver and lung and benign mammary tumors (ATSDR, 2000). IARC has determined that exposure to methylene chloride is "possibly carcinogenic to humans," and the NTP concluded that it is "reasonably anticipated to be a human carcinogen" (IARC, 1999; NTP, 2001). IARC has determined that toluene and xylene are "not classifiable as to their carcinogenicity to humans" in that there was inadequate evidence from studies of humans and animals (IARC, 1999).

Chloroform has produced liver and kidney tumors in a strain-, sex-, species-, and dose-dependent manner and, on the basis of sufficient evidence from animal studies, is "reasonably anticipated to be a human carcinogen" according to the NTP (ATSDR, 1997d; NTP, 2001). Chloroform was once used as an anesthetic, but its association with cancer in nonmedical exposures in humans has not been investigated extensively. The committee did not review studies on the efficacy of solvents as therapeutic agents (see Chapter 2). Chapter 4 provides details on the adverse effects of chloroform as observed in experimental studies.

In addition to evaluating the carcinogenicity of specific chemical agents, IARC has analyzed whether particular occupations pose a greater risk for exposure to carcinogenic agents. In fact, IARC has determined that working in the rubber industry and in boot and shoe manufacturing and repair pose such a risk (IARC, 1987), and it determined that there is "sufficient evidence for the carcinogenicity of occupational exposure as a painter" (IARC, 1989). Although IARC identifies exposures of concerns and specific cancer outcomes that demonstrate an increased risk, its overall charge is to determine whether a specific agent or occupation is carcinogenic, not whether an agent causes a specific cancer outcome. It is important to distinguish the objectives of IARC's program and the charge of the present committee. The purpose of the IARC program is to determine whether agents or occupational exposures are carcinogenic, whereas this committee is charged with determining whether there is an association between exposure to a specific agent and

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chronic human illnesses. As discussed earlier in this report, the committee uses experimental evidence only when it is required by the definitions of the categories of association. Only the category of "Sufficient Evidence of a Causal Association" requires support from experimental evidence. For each conclusion of causality, the animal data that provides a plausible mechanism for the outcome being discussed are described—as in the section on chronic exposure to benzene and acute leukemia. Additional information on the toxicology and available experimental data on a number of solvents reviewed in this report can be found in Chapter 4.

DESCRIPTION OF THE COHORT STUDIES

In reviewing the published epidemiologic literature on exposure to organic solvents, the committee examined a number of occupational cohort studies that provided information on the association between cancer mortality or incidence and exposure to specific organic solvents or to mixtures of organic solvents. Deaths or incident cases of cancer in the cohort studies were recorded, exposed populations were followed over time, and the relationship between rates of cancer and exposure was assessed with statistical methods. Because the cohort studies played an important role in the committee's conclusions and are referred to throughout this chapter, they are described here according to the solvents they examined. Table 6.1 presents for each study a description of the population, the followup period, the number of subjects, the relevant exposures, the methods used to assess exposure to organic solvents, the statistical methods, and the adjustment for potential confounding variables. Similar tables for case–control studies are found in the sections on each type of cancer.

Studies of Workers Exposed to Benzene

Benzene is used in chemical processes often as an intermediate in the manufacture of other chemicals and end products. Occupational exposure to benzene has been studied primarily in industrial workers, including rubber, chemical, and petroleum and gasoline workers. On the basis of human studies of those occupational groups and animal studies over the last 60 years, the allowable occupational health standard for benzene has steadily decreased in the United States. In 1987, the permissible exposure limit (PEL) set by the Occupational Safety and Health Administration (OSHA) was reduced from 10 parts per million (ppm) to a time weighted average over 8 hours (8–hr TWA) of 1 ppm (NIOSH, 1997).

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TABLE 6.1 Description of Cohort Studies Related to Exposure to Organic Solvents

Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Benzene					
NIOSH Pliofilm Cohort					
Infante et al., 1977	Mortality experience (1940–1975) of white male Pliofilm workers (at least 1 day in 1940–1949) at three Goodyear facilities in Ohio	748	(1) US white male population (2) 1447 white, male fibrous-glass construction workers in Ohio	Employment in a benzene-exposed occupation as verified through historical air exposure measurements	SMR Age, time period
Rinsky et al., 1981	Mortality experience (1940–1975) of (1) the original cohort and (2) a second group of white male Pliofilm workers (at least 1 day in 1950–1959) at three Goodyear facilities in Ohio	(1) 748 (2) 258	US white male population	Employment in a benzene-exposed occupation as verified through historical air exposure measurements	SMR Age, sex, time period
Rinsky et al., 1987	Mortality experience (1940–1981) of white male Pliofilm workers (at least 1 day in 1940–1965) at three Goodyear facilities in Ohio	1165	US white male population	Employment in a benzene-exposed occupation as verified through historical air exposure measurements, with cumulative exposure indexes	SMR Age, time period
Paxton et al., 1994a, 1996	Mortality experience (1940–1987) of white male Pliofilm workers (at least 1 day in 1940–1965) at three Goodyear facilities in Ohio	1212	US white male population	Employment in a benzene-exposed occupation as verified through modified historical air exposure measurements, with cumulative exposure indexes	SMR Age, time period
Paxton et al., 1994b	Mortality experience (1940–1987) of white male Pliofilm workers (at least 1 day in 1940–1965) at three Goodyear facilities in Ohio	1868	US white male population	Employment in a benzene-exposed occupation as verified through modified historical air exposure measurements, with cumulative exposure indexes	SMR, Cox proportional hazards model Age, sex, location, time of first Pliofilm employment

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Crump, 1994, 1996	Mortality experience (1940–1987) of white male Pliofilm workers (at least 1 day in 1940–1965) at three Goodyear facilities in Ohio	1717	US white male population	Employment in a benzene-exposed occupation as verified through modified historical air exposure measurements, with cumulative exposure indexes	Life-table analysis Age, sex
Wong, 1995	Mortality experience (1940–1987) of white male Pliofilm workers (at least 1 day in 1940–1965) at three Goodyear facilities in Ohio	1868	US general population	Employment in a benzene-exposed occupation as verified through historical air exposure measurements, with cumulative exposure indexes	SMR Age
Chinese Workers Cohort					
Yin et al., 1987	Mortality experience (1972–1981) of benzene-exposed workers (at least 6 months) in China	28,460 total 15,643 men 12,817 women	28,257 unexposed	Employment in a benzene-exposed occupation as verified through historical air exposure measurements from factory records	RR, SMR Age, sex
Yin et al., 1989	Mortality experience (1972–1981) of benzene-exposed workers (at least 6 months) in China	28,460 total 15,643 men 12,817 women	28,257 unexposed	Employment in a benzene-exposed occupation as verified through historical air exposure measurements from factory records	RR, SMR Age, sex, smoking
Yin et al., 1994	Incidence and mortality experience (1972–1981) of benzene-exposed workers (at least 6 months) in China	28,460 total 15,643 men 12,817 women	28,257 unexposed	Employment in a benzene-exposed occupation as verified through historical air exposure measurements from factory records	SMR, Poisson Age, sex, time of first employment
Li et al., 1994	Incidence and mortality experience (1972–1987) of benzene-exposed workers (at least 1 day) in China	74,828 total 38,833 men 35,995 women	35,805 unexposed	Employment in a benzene-exposed occupation	RR Sex

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Yin et al., 1996a.b	Incidence and mortality experience (1972–1987) of benzene-exposed workers (at least 1 day) in China	74,828 total 38,833 men 35,995 women	35,805 unexposed	Employment in a benzene-exposed occupation as verified through historical air exposure measurements from factory records	RR Age, sex
Hayes et al., 1996	Mortality experience (1972–1987) of benzene-exposed workers (at least 1 day) in China	74,828 total 38,833 men 35,995 women	35,805 unexposed	Employment in a benzene-exposed occupation with cumulative exposure assigned by industrial hygienist from historical records	RR (Poisson), trend analysis Age, sex
Hayes et al., 1997	Incidence (1972–1987) in benzene-exposed workers (at least 1 day) in China	74,828 total 38,833 men 35,995 women	35,805 unexposed	Employment in a benzene-exposed occupation with cumulative and average exposure assigned by industrial hygienist from historical records	RR (Poisson) Age, sex
Other Cohort Studies					
McMichael et al., 1976	Mortality experience (1964–1973) of male rubber workers (at least 1 day) in four plants in Ohio and Wisconsin	18,903	1968 US male population	Employment at one of four rubber-manufacturing plants	SMR Age, race
Wilcosky et al., 1984	Cases, age 40–84 years, selected retrospectively from a cohort of active and retired male rubber workers in a plant in Akron, Ohio, in 1964–1973; an age-stratified, 20% random sample from the original cohort served as the control group	NA	1336 (20% of 6678)	Linkage of worker histories to plant solvent-use records; work in process area with known solvent use equates to exposure Other exposures: trichloroethylene, tetrachloroethylene, toluene, xylenes, naphthas, ethanol, acetone, phenol	Race-specific ORs Age

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Pippard and Acheson, 1985	Mortality experience (1939–1982) of male boot and shoe manufacturers (in 1939) in three towns in Great Britain	5017	County general populations	Job title Other exposures: trichloroethylene, solvents	SMR Age, time period
Wong, 1987a	Mortality experience (1946–1977) of male chemical workers (at least 6 months) in seven US plants	7676	US general population	Job title and employment duration	SMR, Mantel-Haenszel RR Age, race
Wong, 1987b	Mortality experience (1946–1977) of male chemical workers (at least 6 months) in seven US plants	7676	US general population	Job title and employment duration	SMR, Mantel-Haenszel RR Age, race
Paci et al., 1989	Mortality experience (1939–1984) of shoe workers (at least 1 day) in Florence, Italy	2013 total 1008 men 1005 women	Italy general population	Plant production records and work histories	SMR Age, sex, calendar year
Walker et al., 1993	Mortality experience (1940–1982) of shoe-manufacturing workers (at least 1 month in 1940–1979) in Ohio	7814 total 2529 men 5285 women	US general population	Employment at one of two plants Other exposures: MEK, acetone, naphtha, isopropyl alcohol, methanol, ethylene glycol monoethyl ether, xylene	SMR Age, sex, race, time period
Greenland et al., 1994	White, male cases of cancer (multiple sites; died in 1969–1984) and controls in a cohort of transformer-assembly workers in Massachusetts	1821 cases 1202 controls	Internal comparison	Job titles rated for exposure by industrial hygienist Other exposures: trichloroethylene, solvents	Logistic OR (nested case–control) Age, death year, covariates that altered an estimate >20%
Lagorio et al., 1994	Mortality experience (1981–1992) of self-employed gas-station attendants (in 1980) in Italy	2665 total 2308 men 357 women	Latium region, Italy general population	Environmental survey and duration of employment	SMR Age, sex

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Heineman et al., 1995	Brain tumor incidence in women (1980–1984) in Shanghai, China	276	Shanghai general population	Job title	SIR Age
Fu et al., 1996	Mortality experience (1939–1991) of shoe-manufacturing workers in England (1939) and Italy (1950–1984)	6223 total 5220 men 1003 women	England and Italy general populations	Job title	SMR Age, sex, time period
Schnatter et al., 1996a,b	Cases of lymphohematopoietic cancers (died in 1964–1983) and controls in a cohort of Canadian petroleum-distribution workers	29 cases, matched 1:4	Internal comparison	Industrial hygienist review based on work histories, site characterizations, surveys	Mantel-Haenszel OR (nested case–control) Smoking, family cancer history, x-ray history
Ireland et al., 1997	Mortality experience (1940–1991) of male US chemical-plant workers (at least 1 day in 1940–1977) in Monsanto company plant in Sauget, IL	4172	Illinois general population	Industrial hygienist exposure estimates based on work records	SMR
Lynge et al., 1997	Incidence experience (1970–1991) in service-station workers (1970) in Denmark and Scandinavia	18,969 total 16,524 men 2445 women	Nation general populations	Job title	SMR Age, sex
Rushton and Romaniuk, 1997	Cases of leukemia and controls in a cohort of petroleum-distribution workers (1975–1992) in UK	91 cases, matched 1:4	Internal comparison	Measurements factored in occupational hygiene estimates, work histories, job descriptions, fuel compositions	OR (nested case–control), logistic regression Age, smoking, date of hire, employment duration, socioeconomic status

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Trichloroethylene					
Aircraft and Aerospace Workers					
Garabrant et al., 1988	Mortality experience (1958–1982) of aircraft-manufacturing workers (at least 1 day) at an aircraft-manufacturing facility in San Diego County, California (with at least 4 years of cumulative company employment)	14,067 total 11,898 men 2169 women	US general population	Employment determined through company work records and interviews	SMR Age, sex, race, calendar year, duration of employment, year of death
Spirtas et al., 1991	Mortality experience (1952–1982) of aircraft-maintenance workers (at least 1 year in 1952–1956) at Hill Air Force Base in Utah	14,457 total 10,730 men 3727 women	Utah white population	Industrial hygienist assessment from interviews, surveys, hygiene files, position descriptions Other exposures: Stoddard solvent, isopropyl alcohol, trichloroethane, acetone, toluene, MEK, methylene chloride	SMR, trend analysis Age, sex, calendar period
Blair et al., 1998	Incidence and mortality experience (1952–1990) of aircraft-maintenance workers (at least 1 year in 1952–1956) at Hill Air Force Base in Utah	14,457 total 10,730 men 3727 women	Utah white population	Industrial hygienist assessment from interviews, surveys, hygiene files, position descriptions Other exposures: Stoddard solvent, isopropyl alcohol, trichloroethane, acetone, toluene, MEK, methylene chloride	SMR, RR (Poisson) Age, sex, calendar period
Morgan et al., 1998	Mortality experience (1950–1993) of aerospace workers (at least 6 months) Hughes Aircraft plant in Arizona	20,508 total (4733 exposed) 13,742 men 6766 women	US general population	Exposure matrixes generated by employees and industrial hygienists	SMR, Cox proportional hazards model Age, sex

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Boice et al., 1999	Mortality experience (1960–1996) of aircraft-manufacturing workers (at least 1 year) Lockheed Martin facility in California	77,965 total 62,477 men 15,488 women	General California population of white workers	Abstracted from walkthrough surveys, hygiene files, job descriptions Other exposures: tetrachloroethylene, solvents	SMR, RR (Poisson) Age, sex, race, dates of first and last employment
Other Cohort Studies					
Axelson et al., 1978	Mortality experience (1955–1975) of Swedish men occupationally exposed during the 1950s and 1960s	518	Sweden general population	Biologic monitoring for U-TCA	RR Age
Axelson et al., 1994	Mortality experience (1955–1986) of Swedish workers occupationally exposed during the 1950s and 1960s	1670 total 1421 men 249 women	Sweden general population	Biologic monitoring for U-TCA	SMR, SIR (Poisson) Age, sex, time period
Anttila et al., 1995	Incidence experience (1967–1992) of workers biologically monitored for occupational exposure to halogenated solvents (1965–1983) at the Finnish Institute of Occupational Health	3974 total 2050 men 1924 women	Finland general population	Biologic monitoring for U-TCA, and blood metabolites of tetrachloroethylene and trichloroethane Other exposures: trichloroethane, tetrachloroethylene	SIR Age, sex, time period
Ritz, 1999	Mortality experience (1951–1989) of male uranium-processing plant workers (at least 3 years, with first hire in 1951–1972) in Ohio	3814	(1) External comparison with US general population (2) Internal comparison among workers monitored for exposure	Exposure matrixes generated by employees and industrial hygienists	SMR, RR (conditional logistic regression) Age, calendar year, time since first hired, pay type, radiation dose

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Hansen et al., 2001	Incidence experience (1968–1996) in Danish workers (1947–1989) occupationally exposed	803 total 658 men 145 women	Denmark general population	Biologic monitoring for U-TCA	SIR Age, sex, calendar year, period of first employment, employment duration
Tetrachloroethylene					
Dry-cleaning Cohorts					
Brown and Kaplan, 1987	Mortality experience (1960–1982) of dry cleaners (at least 1 year, before 1960) in four US labor unions	1690	US general population	Employment in dry-cleaning shops using tetrachloroethylene or other solvents	SMR Age, time period
Ruder et al., 1994	Mortality experience (1960–1990) of dry cleaners (at least 1 year, before 1960) in four US labor unions	1701 total 592 men 1109 women	SMRs calculated with modified life-table analysis system of NIOSH	Employment in dry-cleaning shops using tetrachloroethylene or other solvents	SMR Age, sex, time period
Ruder et al., 2001	Mortality experience (1960–1996) of dry cleaners (at least 1 year, before 1960) in four US labor unions	1701 total 592 men 1109 women	SMRs calculated with modified life-table analysis system of NIOSH	Employment in dry-cleaning shops using tetrachloroethylene or other solvents	SMR Age, sex, time period
Blair et al., 1990	Mortality experience (1948–1978) of members of a dry-cleaning union in St. Louis	5365 total 1319 men 4046 women	US general population	Exposure index created from job title and length of union membership	SMR, trend analysis Age, sex, calendar year, race
Other Cohort Studies					
Lynge and Thygesen, 1990	Incidence experience (1970–1980) of Danish laundry and dry-cleaning workers (in 1970)	10,600 total 2033 men 8567 women	Denmark general population	Dry-cleaning, job title Other exposures: trichloroethylene, 1,1,2-trichloro-1,2,2-trifluoroethane	SIR Age

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Anttila et al., 1995	Incidence experience (1967–1992) of workers biologically monitored for occupational exposure to halogenated solvents (1965–1983) at the Finnish Institute of Occupational Health	3974 total 2050 men 1924 women	Finland general population	Biologic monitoring Other exposures: trichloroethane, trichloroethylene	SIR Age, sex, time period
Boice et al., 1999	Mortality experience (1960–1996) of aircraft-manufacturing workers (at least 1 year) at Lockheed Martin facility in California	77,965 total 62,477 men 15,488 women	General California population of white workers	Abstracted from walkthrough surveys, hygiene files, job descriptions Other exposures: trichloroethylene, solvents	SMR, RR (Poisson) Age, sex, race, dates of first and last employment
Methylene Chloride *Kodak Park Cohort*					
Friedlander et al., 1978	PMR of former or current exposed workers (1956–1976) at Kodak Park	334	Deaths of former or current unexposed workers (1956–1976) at Kodak Park	Employment in methylene chloride area	PMR, SMR Age, sex
	Mortality experience (1964–1976) of hourly-wage male workers (in 1964) at Kodak Park	751	Hourly-wage male workers at Kodak Park and in New York state (excluding New York City) men		
Hearne and Friedlander, 1981	Mortality experience (1964–1980) of hourly-wage male workers (in 1964) at Kodak Park	750	Hourly-wage male workers at Kodak Park and in New York state (excluding New York City) men	Employment in methylene chloride area	SMR Age, sex

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Hearne et al., 1987	Mortality experience (1964–1984) of hourly-wage male workers (in 1964) at Kodak Park	1013	(1) New York state (excluding New York City) men (1945–1990) (2) Over 40,000 Rochester-based Kodak workers	Employment in roll-coating division, cumulative exposure assigned by industrial hygienist from historical records	SMR Age, sex, time period
Hearne et al., 1990	Mortality experience (1964–1988) of hourly-wage male workers (in 1964) at Kodak Park	1013	(1) New York state (excluding New York City) men (1945–1990) (2) Over 40,000 Rochester-based Kodak workers	Employment in roll-coating division, cumulative exposure assigned by industrial hygienist from historical records	SMR, trend analysis Age, sex, time period
Hearne and Pifer, 1999	Mortality experience (1946–1994) of two overlapping cohorts of exposed male workers (at least 1 year in 1946–1970; any employment in 1964–1970) at Kodak Park	(1) 1311 (2) 1013	New York state (excluding New York City) men (1945–1990)	Employment in methylene chloride area, cumulative exposure assigned by industrial hygienist from historical records	SMR, trend analysis Age, sex, time period
Cellulose-Fiber Production Cohort					
Ott et al., 1983	Mortality experience (1954–1977) of cellulose-fiber production plant workers (at least 3 months) in Rock Hill, SC	1271 total 551 men 720 women	York County, SC, general population	Employment in plant, comprehensive industrial hygienist survey Other exposures: acetone, methanol	SMR, conditional risk, Cox regression Age, sex, race, year of first exposure
Lanes et al., 1990	Mortality experience (1954–1986) of cellulose-fiber production plant workers (at least 3 months in 1954–1977) in Rock Hill, SC	1271 total 551 men 720 women	York County, SC, general population	Employment in plant, comprehensive industrial hygienist survey Other exposures: acetone, methanol	SMR Age, sex, race

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Lanes et al., 1993	Mortality experience (1954–1990) of cellulose-fiber production plant workers (at least 3 months in 1954–1977) in Rock Hill, SC	1271 total 551 men 720 women	York County, SC, general population	Employment in plant and comprehensive industrial hygienist survey Other exposures: acetone, methanol	SMR Age, sex, race
Other Cohort Studies					
Gibbs et al., 1996	Mortality experience (1970–1989) of cellulose-fiber production workers (at least 3 months) in Cumberland, MD	3211 total 2187 men 1024 women	Allegheny County, MD, general population	Workplace monitoring data, job title	SMR Age, sex, race, time period
Tomenson et al., 1997	Mortality experience (1946–1994) of male cellulose triacetate film-base workers (any employment in 1946–1988) in Brantham, UK	1785	England and Wales mortality rates	Workplace monitoring	SMR, trend analysis Age, time period
Toluene and Xylene					
Swedish Paint Industry Cohort					
Lundberg, 1986	Incidence and mortality experience (1955–1981) of male, Swedish paint-industry workers (at least 5 years in 1955–1975) with long-term exposure to organic solvents	416	Sweden general population	Industry employment, historical air exposure measurements	SMR Sex, time period
Lundberg and Milatou-Smith, 1998	Incidence and mortality experience (1955–1994) of male, Swedish paint-industry workers (at least 5 years in 1955–1975) with long-term exposure to organic solvents	411	Sweden general population	Industry employment, historical air exposure measurements	SMR, SIR Age, sex, time period
Other Cohort Studies					
Anttila et al., 1998	Incidence experience (1973–1992) in workers biologically monitored for occupational exposure to aromatic hydrocarbons (1973–1983) at the Finnish Institute of Occupational Health	5301 total 3922 men 1379 women	Finland general population	Biologic monitoring	SIR Age, sex, time period

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Svensson et al., 1990	Incidence and mortality experience (1925–1985) of Swedish male rotogravure workers (at least 3 months)	1020	Population-specific rates for geographic area around factory	Exposures evaluated through plant visits, biologic monitoring, workplace measurements, historical documents, interviews Other exposures: benzene, solvents	SMR, SIR Age, sex, calendar year, location
Solvents					
UK Rubber Worker Cohort					
Parkes et al., 1982	Mortality experience (1946–1975) of UK male rubber workers (at least 1 year in 1946–1960)	33,815	UK general population	Industry employment	SMR Age, sex
Sorahan et al., 1986	Mortality experience (1946–1980) of UK male rubber workers (at least 1 year in 1946–1960)	36,445	UK general population	Industry employment	SMR, regression models and life tables Age, sex, age at hire, entry cohort, location, work sector
Sorahan and Cathcart, 1989	Mortality experience (1946–1985) of UK male rubber workers (at least 1 year in 1946–1960)	36,691	UK general population	Industry employment	SMR, regression models and life tables Age at hire, entry cohort, location, work sector, duration of employment

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Other Cohort Studies					
Costantini et al., 1989	Mortality experience (1950–1983) of male workers at tanneries (at least 6 months) in Tuscany, Italy	2926	Italy general population	6 months of employment	SMR Age, time period
Guberan et al., 1989	Incidence and mortality experience (1970–1984) of painters and electricians (in 1970) in the Canton of Geneva	1916 painters 1948 electricians	Switzerland regional population	Job title	SMR, SIR Age
Acquavella et al., 1993	Mortality experience (1950–1987) of workers hired at a metal components manufacturing facility (at least 6 months in 1950–1967) in Iowa	3630 total 2664 men 966 women	Iowa general population	Occupational titles, departments	SMR, RR Age, sex, time period
Berlin et al., 1995	Incidence and mortality experience (1967–1987) of Swedish workers occupationally exposed to solvents	5791 total 5283 men 508 women	Sweden general population	Patients with solvent-related disorders	SMR, SIR Age, sex
Lynge et al., 1995	Incidence experience (1970–1987) in Danish printing workers (in 1970)	19,127 total 15,534 men 3593 women	Economically active people in Denmark	Job title	SIR Age, alcohol and tobacco use
Steenland and Palu, 1999	Mortality experience (through 1994) of members of US painters unions (at least 1 year of membership; born before 1940) in four states	42,170	US general population, nonpainter cohort	Union membership	SMR, SRR Age, time period
Other Specific Solvents					
Isopropyl Alcohol and Methyl Ethyl Ketone					
Alderson and Rattan, 1980	Mortality experience (1935–1975) of workers in Shell MEK dewaxing or isopropyl alcohol plants (at least 1 year) in Britain	262 IAP 446 MEK	US general population	Employment in one of two plants	SMR Age, time period
Phenol					
Dosemeci et al., 1991	Mortality experience (1966–1979) of white male workers (employed before 1966) employed at five facilities producing or using phenol and formaldehyde	14,861	US general population	Employment at one of five facilities	SMR Age, time period

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Reference	Description	Study Group (*N*)	Comparison Group (*N*)	Exposure Assessment and Other Relevant Exposures	Analysis and Adjustment for Potential Confounders
Ethanol and Isopropyl Alcohol					
Teta et al., 1992	Mortality experience (1940–1983) of male isopropanol and ethanol production workers (1940–1978) at two facilities in South Charleston, WV, and Texas City, TX	1031	(1) White subjects and South Charleston cohort compared with general US white male population (2) Nonwhite subjects from Texas compared with US nonwhite male population	Employment in one of two plants	SMR Age, time period, duration of assignment, time since first assignment, year of first assignment, type of assignment

NOTE: SMR = standardized mortality ratio; RR = relative risk; SIR = standardized incidence ratio; OR = odds ratio; PMR = proportional mortality ratio; SRR = standardized relative risk; NIOSH = National Institute for Occupational Safety and Health; IAP = isopropyl alcohol; MEK = methyl ethyl ketone; U-TCA = urinary metabolite of trichloroethylene.

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Although the association between benzene and cancer was assessed in a number of cohort studies, two studies provide the most comprehensive data. The first was designed to investigate mortality in three Ohio rubber-manufacturing plants, referred to as the "Pliofilm" cohort (Crump, 1994, 1996; Infante et al., 1977; Paxton, 1996; Paxton et al., 1994a,b; Rinsky et al., 1987; Wong, 1995). Benzene was used in the production of rubber hydrochloride, a natural rubber cast film used primarily for wrapping foods and marketed under the trade name Pliofilm. The plants were chosen because of the relatively high exposure to benzene and the lack of other toxic chemicals in use. In 1975, after a report of several leukemia cases, the National Institute for Occupational Safety and Health conducted a retrospective study of 748 Pliofilm workers who were exposed to benzene (Infante et al., 1977). Rinsky and colleagues (1981, 1987) expanded on the work of Infante and colleagues by increasing the size of the cohort to 1006 workers, extending the years of observation, and collecting additional exposure data from the plants' processes, company records, and air-sampling data (Rinsky et al., 1981), thereby providing estimates of exposure for each job in the various areas of the plant (Rinsky et al., 1987). The retrospective exposure assessment was further modified by Crump and Allen (1984) and Paustenbach and colleagues (1992). Crump and Allen (1984) developed an exposure matrix based on the concept that the benzene levels in the workplace may have improved over time, whereas the exposure matrix developed by Paustenbach and colleagues (1992) incorporated more detailed information from monitoring devices, the changing length of the workweek over the years, the impact of World War II on production, engineering controls, and other available and experimental data to assess exposure to benzene. Considerable controversy surrounds the assessments of exposure (Wong, 1995). Different authors have used the different exposure assessments in their analyses: the Rinsky exposure assessment (Paxton et al., 1994a,b; Rinsky et al., 1981, 1987), the Crump assessment (Paxton et al., 1994a,b), and the Paustenbach assessment (Crump, 1994; Paxton et al., 1994a,b). The differences in the exposure assessments lead to differences in the estimates of relative risks for various sites of cancer according to exposure to benzene. The differences in relative risk are important in setting regulatory standards but were not sufficiently different to affect the committee's determination of the magnitude of association.

The second key study of occupational exposure to benzene was conducted in China. After conducting a nationwide benzene-monitoring survey in China during 1979–1981, Yin and colleagues at the Chinese Academy of Preventive Medicine identified a cohort of about 30,000 workers who were occupationally exposed to benzene or mixtures containing benzene (Yin et al., 1987). Subjects were selected from painting, shoe-making, rubber synthesis, leather, and adhesive and organic-chemical synthesis factories. A sample of 28,257 workers employed in machine production, textile, and cloth factories was taken to represent an unexposed comparison population. Later studies expanded the original cohort to 74,828 benzene-exposed and 35,805 nonexposed workers and included a detailed assessment of exposure to benzene. Those studies were conducted in collaboration with the US National Cancer Institute (Hayes et al., 1996, 1997; Li et al., 1994; Yin et al., 1987, 1989, 1994, 1996a,b). Like the Pliofilm study, studies of the cohort yielded valuable information regarding the risk of developing or dying from cancer in relation to exposure to benzene.

Other important cohort studies of benzene-exposed workers include those of American chemical workers (Ireland et al., 1997; Wong, 1987a,b), female workers in China

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(Heineman et al., 1995), other rubber-plant workers (McMichael et al., 1976; Wilcosky et al., 1984), shoe-manufacturing workers (Fu et al., 1996; Paci et al., 1989; Pippard and Acheson, 1985; Walker et al., 1993), transformer-assembly workers (Greenland et al., 1994), filling and service-station attendants (Lagorio et al., 1994, Lynge et al., 1997), and petroleum distributors (Rushton and Romaniuk, 1997; Schnatter et al., 1996a,b). These studies differed substantially from the two preceding studies in that exposure was much lower. For example, levels in the Pliofilm cohort ranged from 7.2 to 24.9 ppm (Rinsky et al., 1981, 1987), whereas levels in the cohort of petroleum workers ranged from 0.01 to 6.2 ppm (Ireland et al., 1997; McMichael et al., 1976; Rushton and Romaniuk, 1997; Schnatter et al., 1996a,b).

Studies of Workers Exposed to Trichloroethylene

The most important use of trichloroethylene has been in the removal of greases, tars, and oils from metal parts. It has also been used by the textile industry to scour cotton, wool, and other fabrics and as a solvent in waterless dying and finishing operations (ATSDR, 1997b). The regulatory limit set by OSHA is a 8–hr TWA of 100 ppm (NIOSH, 1997).

Mortality in relation to exposure to trichloroethylene has been examined in four large cohort studies of aircraft and aerospace manufacturing and maintenance workers (Blair et al., 1998; Boice et al., 1999; Garabrant et al., 1988; Morgan et al., 1998). In general, industrial hygienists reviewed information obtained from walkthrough surveys, interviews of long-term employees, and historical information on job titles and tasks, operations, and worksites to classify workers by duration and intensity of exposure. The first study was conducted to evaluate mortality rates among 14,457 aircraft maintenance workers at Hill Air Force Base, Utah, in response to concerns expressed by workers in the middle-1970s about potential health effects of chemical exposure (Spirtas et al., 1991). Trichloroethylene was used as a vapor degreaser until 1978, when it was replaced with 1,1,1-trichloroethane. It was also used to clean small electric parts at work benches until 1968 (Blair et al., 1998). Other solvents used at the base were primarily other chlorinated hydrocarbons, aromatic hydrocarbons, and carbon tetrachloride. Blair and co-workers (1998) extended the followup of the cohort assembled by Spirtas and colleagues (1991) by 8 years. The estimates of exposure developed for the initial cohort study (Stewart et al., 1991) were also used in the extended followup study.

Two additional large cohort studies evaluated mortality in aircraft manufacturing facilities where trichloroethylene was commonly used as a degreaser. Boice and colleagues (1999) investigated 77,965 workers at Lockheed Martin's Burbank California factories, and Morgan and co-workers (1998) reported on 20,508 employees at a Hughes Aircraft manufacturing facility in Arizona.

Other important but smaller cohort studies of workers exposed to trichloroethylene are those of Swedish trichloroethylene production workers (Axelson et al., 1978, 1994), US uranium processing-plant workers (Ritz, 1999), and other workers occupationally exposed to trichloroethylene in Finland (Anttila et al., 1995) and Denmark (Hansen et al., 2001). Exposure–response analyses in the Scandinavian studies were based on biologic monitoring of urinary-trichloroacetic acid (U-TCA, a metabolite of trichloroethylene) measured in urine samples from workers (Anttila et al., 1995; Axelson et al., 1978, 1994; Hansen et al., 2001). Hansen and colleagues (2001) also used data on levels of trichloroethylene in the breathing

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zone of workers. The US study used semiquantitative exposure estimates based on expert review (Ritz, 1999).

Studies of Workers Exposed to Tetrachloroethylene and Dry-cleaning Solvents

Tetrachloroethylene has been used for metal cleaning and vapor degreasing and for dry-cleaning and textile processing. The PEL set by OSHA is a 8–hr TWA of 100 ppm (NIOSH, 1997).

Occupational exposure to tetrachloroethylene has been studied primarily in dry-cleaning workers because of its widespread use. Dry-cleaning workers are extensively exposed to organic solvents, which are integral to the dry-cleaning process. The evolution of the dry-cleaning process has seen the use of a variety of solvents. Most of the early dry-cleaning solvents were petroleum-based and included naphtha and Stoddard solvent. The petroleum-based solvents were replaced in the 1930s largely with carbon tetrachloride, a less expensive alternative (IARC, 1995). Information about the toxicity and corrosiveness of carbon tetrachloride led to its replacement in the 1950s with chlorinated hydrocarbons. Today, tetrachloroethylene is the most commonly used dry-cleaning solvent in the United States. Other solvents and chemicals used in dry-cleaning include 1,1,2-trichloro-1,2,2-trifluoroethane, and 1,1,1-trichloroethane (IARC, 1995).

An important study examined a cohort of 1708 US dry-cleaning workers drawn from four labor unions, first reported by Brown and Kaplan (1987), and updated by Ruder and colleagues (1994, 2001). The original study investigated mortality through 1982, the first update extended the followup through 1990 (Ruder et al., 1994), and the most recent study updated mortality through 1996 (Ruder et al., 2001). In the updates, two subcohorts were evaluated on the basis of employment in shops where tetrachloroethylene was the cleaning solvent (625 workers) or in shops where tetrachloroethylene use could not be confirmed or another solvent was used as the cleaning solvent (1083 workers).

Another study, of 5365 members of a dry-cleaning union in Missouri, assessed mortality in relation to estimated levels of exposure to dry-cleaning solvents (Blair et al., 1990). Exposure indexes were based on job title and type of establishment. Information on the type of solvent used was not available so workers who specifically used tetrachloroethylene could not be identified.

Other studies of exposure to tetrachloroethylene and cancer include a US study of aircraft manufacturing workers (Boice et al., 1999) and a Finnish study of workers occupationally exposed to three halogenated hydrocarbons, including tetrachloroethylene (Anttila et al., 1995). The exposure assessment of the US study was based on expert review of walkthrough surveys and historical documents and other approaches (Boice et al., 1999), whereas the Finnish study estimated level of exposure from biologic monitoring (Anttila et al., 1995). Another study examined Danish laundry and dry-cleaning workers whose chemical exposure was inferred from their occupations, as specified by census industry codes (Lynge and Thygesen, 1990).

Studies of Workers Exposed to Methylene Chloride

Methylene chloride (dichloromethane) has been used in degreasing, in paint stripping, as an aerosol propellant, and in the manufacture of textiles, plastics, and photographic film. A large proportion of workers exposed to methylene chloride are

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involved in metal cleaning, industrial paint stripping, and using ink solvents (ATSDR, 2000). The regulatory limits have decreased as information on toxicity has accumulated (ATSDR, 2000). The current PEL set by OSHA is a 8–hr TWA of 25 ppm (NIOSH, 1997).

The key occupational cohort study of exposure to methylene chloride was an incidence and mortality study of workers in an Eastman Kodak plant (Friedlander et al., 1978; Hearne and Friedlander, 1981; Hearne and Pifer, 1999; Hearne et al., 1987, 1990). The workers, ranging in number from 750–1311, were exposed chronically to methylene chloride in the manufacturing of cellulose triacetate, a photographic film base, as confirmed by study personnel who used air sampling and gas chromatography. In the most recent update, Hearne and Pifer (1999) followed the mortality experience through 1994 for two groups of workers: 1311 workers who first worked in film-support manufacturing and related operations in 1946–1970 and the Roll Coating Cohort (1964–1970) of 1013 employees that was previously studied (Hearne et al., 1987, 1990). Exposure to methylene chloride was estimated by combining air-monitoring data with information on work histories.

Other important studies include a study of workers employed at a plant that produced cellulose triacetate film base in the UK (Tomenson et al., 1997), and studies of workers in the production of cellulose fiber at a Hoechst manufacturing plant in South Carolina (Lanes et al., 1990, 1993; Ott et al., 1983) and a Hoechst plant in Maryland (Gibbs et al., 1996). Estimates of exposure in the UK cohort were derived from area-monitoring results, work histories, and historical information on production processes (Tomenson et al., 1997). Some exposure-monitoring data were obtained on the South Carolina cohort in the 1970s (Ott et al., 1983), but exposure estimates were unavailable for most of the study period. Exposure measurements were not used in the mortality analysis of the South Carolina cohort (Lanes et al., 1990, 1993), but Gibbs and co-workers (1996) used the available exposure data to determine high and low exposure ranges.

Studies of Workers Exposed to Other Specific Solvents

Three studies of solvent-production plants were used to evaluate mortality in relation to exposure to specific solvents: isopropanol (Alderson and Rattan, 1980; Teta et al., 1992), methyl ethyl ketone (Alderson and Rattan, 1980), phenol (Dosemeci et al., 1991), and toluene, xylene, and styrene (Anttila et al., 1998). The main uses of isopropanol are as a chemical intermediate and in applications in medicine and industry (Logsdon and Loke, 1996). The PEL is a 8–hr TWA of 400 ppm (NIOSH, 1997). Methyl ethyl ketone is used primarily as a solvent in industry. The regulatory limit set by OSHA is 200 ppm (NIOSH, 1997). Phenol is commonly used in the production of epoxy resins and polycarbonates, phenolic resins and molding compounds, caprolactam, aniline alkylphenols, and xylenols; as a fungicide or disinfectant; and in a variety of medications (ATSDR, 1998; Wallace, 1996). The occupational exposure limit set by OSHA is a 8–hr TWA of 5 ppm (NIOSH, 1997). Toluene and xylene are used in the manufacture of a variety of chemicals and as solvents for paints, lacquers, gums, printing inks, and resins. Styrene is used in the production of polystyrene plastics and resins and as an intermediate in the production of such copolymers as styrene–acrylonitrile, acrylonitrile–butadiene–styrene, and styrene–butadiene rubber. The occupational regulatory limit for toluene is a 8–hr TWA of 200 ppm (NIOSH, 1997), and the PEL for xylene and styrene is a 8–hr TWA of 100 ppm (NIOSH, 1997).

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The key studies for evaluating risks posed by those solvents include the following. Alderson and Rattan (1980) evaluated mortality in 262 male workers employed in isopropanol plant and 446 male employees of two methyl ethyl ketone dewaxing plants, using the type of plant as an indicator of exposure. Teta and colleagues (1992) conducted a cohort mortality study of 1031 workers employed at two facilities that produced ethanol and isopropanol. Employment in an isopropanol strong-acid production unit was used as an exposure surrogate for isopropanol. Dosemeci and co-workers (1991) conducted a mortality followup of 14,861 workers employed in five plants that manufactured or used phenol and formaldehyde. Estimates of exposure to phenol were derived from expert review of information obtained from walkthrough survey reports, historical monitoring results, and other workplace information. Anttila and colleagues (1998) investigated 3922 male and 1379 female Finnish workers occupationally exposed to toluene, xylene, and styrene; level of exposure was determined from biologic monitoring (Anttila et al., 1995).

Studies of Workers Exposed to Unspecified Mixtures of Organic Solvents

Solvents are used in numerous occupations, so the committee examined cancer mortality and incidence in workers in a number of occupations that may have involved exposure to organic solvents. It is important to note that workers in the occupations in question have potential exposure to numerous chemicals in addition to solvents.

Painters have the potential for frequent and high level exposure to many types of organic solvents. Organic solvents, such as, toluene, xylene, glycols, and methylene chloride, have been used over the years in the composition of paint, paint thinners, cleaners, and strippers. Painters are exposed to numerous other chemical and environmental agents, including pigments, dusts, resins, and silicates. In most instances, it was not possible to identify which solvents were used, and the committee referred to them as unspecified mixtures of organic solvents. Lundberg and Milatou-Smith (1998) evaluated cancer mortality and incidence in a cohort of 411 male workers who had been employed for more than 5 years in 1955–1975 in the Swedish paint-manufacturing industry (followup of Lundberg, 1986). Guberan and colleagues (1989) studied cancer mortality and incidence in 1916 painters in Geneva, Switzerland, who were identified from the 1970 census. The largest cohort study of painters was conducted by Steenland and Palu (1999), who evaluated mortality patterns in a cohort of 42,170 painters who were members of the Painters Union for 1 year or more before 1979.

Other cohorts exposed to unspecified chemical mixtures involve printers (Lynge et al., 1995; Svensson et al., 1990); workers in solvent-production plants (Berlin et al., 1995); metal workers (Acquavella et al., 1993); rubber workers (Parkes et al., 1982; Sorahan and Cathcart, 1989; Sorahan et al., 1986); workers in tanneries (Costantini et al., 1989); and shoemakers (Fu et al., 1996; Paci et al., 1989; Pippard and Acheson, 1985; Walker et al., 1993). In the past, some shoemaking cohorts would have had considerable exposure to benzene (e.g., Fu et al., 1996; Paci et al., 1989). However, because the composition of glues has changed, benzene being replaced with other solvents, and because there were no precise estimates of exposure, the committee classified those cohorts as being exposed to unspecified mixtures of organic solvents.

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ORAL, NASAL, AND LARYNGEAL CANCER

Description of Case–Control Studies

Two case–control studies reviewed by the committee that included oral, nasal, or laryngeal cancers are described in Table 6.2. One population-based case–control study examined the risk of nasal and nasopharyngeal cancer associated with occupational exposure to organic solvents (Hardell et al., 1982), and a second examined the risk of oral cavity and laryngeal cancers associated with work in the dry-cleaning industry (Vaughan et al., 1997). Both included interviews with study subjects concerning occupational history. In the former study, exposure to organic solvents was self-reported; in the latter, levels of exposure to tetrachloroethylene in cleaning jobs were assigned by an industrial hygienist.

Epidemiologic Studies of Exposure to Organic Solvents and Oral Cancer

Three cohort studies and one case–control study failed to provide strong evidence of an association between tetrachloroethylene and dry-cleaning solvents and oral cancer. Ruder and colleagues (2001) found a strong, increased risk of cancer of the tongue (standardized mortality ratio [SMR] = 9.03, 95% confidence interval [CI] = 1.86–26.39) in the subcohort exposed only to tetrachloroethylene. In another cohort of dry cleaners, Blair and colleagues (1990) found no increased risk of cancers of the buccal cavity and pharynx (SMR = 1.0, 95% CI = 0.3–2.2).

The case–control study undertaken by Vaughan and colleagues (1997) found little evidence of an increased risk of oral cancer in dry-cleaning workers (odds ratio $[OR]_{\text{possible exposure}} = 1.2$, 95% CI = 0.3–4.6; $OR_{\text{probable exposure}} = 1.5$, 95% CI = 0.2–9.5). The relative risks increased with increasing cumulative exposure but not with duration of employment, although there was considerable statistical uncertainty in the trend.

In only one study was the risk of cancers of the mouth and throat evaluated among workers exposed to phenol (Dosemeci et al., 1991); no increased risk was found (SMR = 0.8, 95% CI = 0.4–1.5).

The risk of oral cancer in industries exposed to solvents was estimated in cohorts of workers in cellulose-fiber production (Lanes et al., 1990), shoe manufacture (Walker et al., 1993), methyl ethyl ketone dewaxing (Alderson and Rattan, 1980), and ethanol and isopropanol production (Teta et al., 1992). Although specific solvents were used in most of those occupations, many other solvents were also used, and specific solvents were not evaluated in any of the studies. There was no evidence of positive associations in any of these studies.

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TABLE 6.2 Description of Case–Control Studies of Oral, Nasal, and Laryngeal Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Hardell et al., 1982	Male cases, age 28–85 years, reported to the Swedish Cancer Registry in 1970–1979 from the three northernmost counties of Sweden; controls from authors' previous studies on soft tissue sarcoma and malignant lymphoma were used; controls identified from the Swedish National Population Registry and the National Registry for Causes of Death	44 nasal 27 nasopharyngeal	541	Organic solvents	Occupational histories (job titles) and exposures (self-reported) obtained through questionnaire and supplemented by telephone interview (direct or proxy)	Exposure frequency	None
Vaughan et al., 1997	Cases, age 20–74 years when diagnosed, identified from a cancer surveillance system covering 13 counties in western Washington; cases lived in one of the three largest counties and were diagnosed in 1983–1990; population-based controls, frequency-matched by age and sex, identified through RDD Response rates: 85.2 % of oral cavity cancer cases, 80.8% of laryngeal cancer cases, 80.3% of controls	491 oral cavity 235 laryngeal	724	Tetrachloroethylene Dry-cleaning work	In-person interviews to assess employment and duration in dry-cleaning occupations; probability of exposure from decade of employment; cumulative exposure measurements calculated by duration and occupation-specific time-weighted averages	Conditional logistic regression	Age, sex, education, study period, alcohol consumption, cigarette smoking, race

NOTE: RDD = random-digit dialing.

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Summary and Conclusion

There was little consistent evidence of an association between oral cancer and exposure to tetrachloroethylene and dry-cleaning solvents. Although there were several positive studies, most were based on small numbers of exposed cases and did not have sufficient statistical power. For exposure to phenol, only one study was identified and a risk of oral cancer was not found. No risk was also found among the occupational studies on solvent mixtures. Table 6.3 identifies the studies reviewed on oral cancer. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and oral cancer.

TABLE 6.3 Selected Epidemiologic Studies—Oral Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific and Unspecified Mixtures of Organic Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	Dry-cleaning union workers exposed to tetrachloroethylene		
	Cancer of the tongue	3	9.03 (1.86–26.39)
Walker et al., 1993	Ohio shoe-manufacturing employees		
	Males and females	5	0.67 (0.22–1.59)
Teta et al., 1992	Male workers at ethanol/isopropanol production plants		
	South Charleston	2	1.3 (0.2–4.8) [a]
	Texas City	1	1.4 (0.0–8.4) [a]
Dosemeci et al., 1991	Male industrial workers exposed to phenol	11	0.8 (0.4–1.5)
Blair et al., 1990	St. Louis, MO, dry-cleaning workers	5	1.0 (0.3–2.2)
Lanes et al., 1990	Cellulose-fiber production workers	2	2.31 (0.39–7.60)
Alderson and Rattan, 1980	Male British workers at two methyl ethyl ketone dewaxing plants	2	15.38 (1.86–55.54) [a]
Case–Control Study			
Vaughan et al., 1997	Oral cancer among dry-cleaning workers		
	Possible exposure to tetrachloroethylene	7	1.2 (0.3–4.6)
	Probable exposure to tetrachloroethylene	4	1.5 (0.2–9.5)
	Cumulative exposure to tetrachloroethylene (ppm-years)		
	1–29 ppm-years	3	1.0 (0.1–7.0)
	30+ ppm-years	4	1.4 (0.2–8.7)
	Duration of employment		
	1–9 years	6	1.4 (0.3–5.7)
	10+ years	1	0.4 (0.0–31.6)

[a]Risk estimate and 95% CI calculated by the committee using standard methods from the observed and expected numbers presented in the original study.

Epidemiologic Studies of Exposure to Organic Solvents and Nasal Cancer

Few studies with sufficient numbers of cases to assess the relationship between exposure to benzene and oral cancer were available. The cohort study by Yin and colleagues (1996a) of

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benzene-exposed workers in China showed an increased risk of nasopharyngeal cancer among male workers (relative risk [RR] = 2.1, 95% CI = 0.7–9.3). The RR was 2.4 (95% CI = 0.8–10.5).

A cancer mortality study of shoe-manufacturing workers by Fu and colleagues (1996) analyzed the risk associated with exposure to solvents (found mostly in glues) and leather dusts in two cohorts of shoemakers in England and Florence, Italy. Risk of nasal cancer from occupational exposures was strongly increased (SMR = 7.41, 95% CI = 3.83–12.94) in the English cohort (only one death from nasal cancer was found in the Florence cohort). Exposure was assessed by using job titles, and no specific exposures were identified. It is not clear whether solvents, leather dust, or other agents contributed to the increased risk of nasal cancer.

Hardell and colleagues (1982) conducted a case–control study of nasal and nasopharyngeal cancers and exposure to various agents, including solvents. Although they provided no estimates of relative risk, the committee calculated relative risks and CIs from the raw data provided and found weak associations with exposure to high-grade organic solvents (nasal: OR = 1.24, 95% CI = 0.51–2.91; nasopharyngeal: OR = 1.27, 95% CI = 0.47–3.68).

Summary and Conclusion

The only study on exposure to benzene and risk of nasal cancer had a highly imprecise estimate of effect. Other studies are needed to determine whether an association exists. For exposure to solvent mixtures, the English shoemaker study showed a strong association. However, the Swedish case–control study (Hardell et al., 1982) did not corroborate those findings. Table 6.4 identifies the studies reviewed by the committee on nasal cancer. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and nasal cancer.

TABLE 6.4 Selected Epidemiologic Studies—Nasal Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific and Unspecified Mixtures of Organic Solvents			
Cohort Studies—Mortality			
Yin et al., 1996a	Chinese workers exposed to benzene		
	Male	12	2.1 (0.7–9.3)
	Total	14	2.4 (0.8–10.5)
Fu et al., 1996	Shoemakers in England and Florence		
	English cohort	12	7.41 (3.83–12.94)
	Florence cohort	1	9.09 (0.23–50.65)
Alderson and Rattan, 1980	Male British workers at an isopropyl alcohol plant	1	50.0 (1.3–278.5)[a]
Case–Control Study			
Hardell et al., 1982	Male cases exposed to high-grade organic solvents		
	Nasal	8	1.24 (0.51–2.91)[a]
	Nasopharyngeal	5	1.27 (0.47–3.68)[a]

[a]Risk estimate and 95% CI calculated by the committee using standard methods from the observed and expected numbers presented in the original study.

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Epidemiologic Studies of Exposure to Organic Solvents and Laryngeal Cancer

In a cohort of dry cleaners, Blair and colleagues (1990) found 60% excess mortality from laryngeal cancers (SMR = 1.6, 95% CI = 0.3–4.7). In a case–control study of laryngeal cancer, Vaughan and colleagues (1997) found an association with possible exposure to tetrachloroethylene among dry cleaners (OR = 2.3; 95% CI = 0.5–10.2) but not among those probably exposed (OR = 0.9, 95% CI = 0.1–12.9). Risk increased with duration of employment in the dry-cleaning industry but not with increasing cumulative exposure.

Cohorts of workers in ethanol and isopropanol production (Teta et al., 1992) and shoe manufacture (Walker et al., 1993) were evaluated for their cancer mortality, and there was little evidence of an association (total of three exposed deaths).

Summary and Conclusion

For exposure to tetrachloroethylene and dry-cleaning solvents and risk of laryngeal cancer, both studies' findings were based on very few exposed cases, and this resulted in imprecise estimates of relative risk. Similarly, the studies on solvent mixtures were limited by the small number of exposed cases and lack of positive findings. As a result, there was insufficient evidence to conclude that there were associations between exposure to specific solvents or solvent mixtures and laryngeal cancer. The studies reviewed by the committee are identified in Table 6.5. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and laryngeal cancer.

TABLE 6.5 Selected Epidemiologic Studies—Laryngeal Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Specific and Unspecified Mixtures of Organic Solvents			
Cohort Studies—Mortality			
Walker et al., 1993	Ohio shoe manufacturing employees		
	Females	2	3.34 (0.40–12.09)
Teta et al., 1992	Male workers at ethanol/isopropanol production plants		
	South Charleston	1	1.4 (0.0–8.0) [a]
	Texas City	1	3.3 (0.1–18.6) [a]
Blair et al., 1990	St. Louis, MO, dry-cleaning workers	3	1.6 (0.3–4.7)
Case–Control Study			
Vaughan et al., 1997	Laryngeal cancer among dry-cleaning workers		
	Possible exposure to tetrachloroethylene	4	2.3 (0.5–10.2)
	Probable exposure to tetrachloroethylene	1	0.9 (0.1–12.9)
	Cumulative exposure to tetrachloroethylene (ppm-years)		
	1–29 ppm-years	2	2.0 (0.2–17.9)
	30+ ppm-years	2	2.5 (0.3–19.1)
	Duration of employment		
	1–9 years	3	1.9 (0.3–10.2)
	10+ years	2	5.5 (0.4–75.0)

[a]Risk estimate and 95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.

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GASTROINTESTINAL TRACT TUMORS

Description of Case–Control Studies

Several case–control studies were used to evaluate the risks of cancer at gastrointestinal sites in relation to occupational exposures (Table 6.6), and one study was used to assess the risk of colorectal and pancreatic cancers posed by exposure to tetrachloroethylene in drinking water (Paulu et al., 1999).

All the studies but one used interviews with subjects to assess occupational history and in some cases occupational exposures; one study used self-administered questionnaires of next of kin (Kauppinen et al., 1995). The response rates in the latter study were 50% or less, so the results were unlikely to be representative of the entire study population. There were four reports (Dumas et al., 2000; Gérin et al., 1998; Goldberg et al., 2001; Parent et al., 2000) of one multisite case–control study conducted in Montreal in the 1980s. The novel features of the study include use of a mixed control population (cancer and population controls), in-depth interviews to obtain details of each job of each subject, translation of the interviews by a team of industrial hygienists and chemists into semiquantitative indexes of exposure to about 300 physical and chemical agents, and good information on potential confounding factors. Ekstrom and colleagues (1999) investigated gastric cancer and also used experts to attribute exposure on the basis of questionnaires. The study by Paulu and colleagues (1999) of colorectal and pancreatic cancers used estimates of exposure to tetrachloroethylene in drinking water.

Alcohol is a risk factor for esophageal cancer, and this requires consideration in evaluating the association between solvent exposure and esophageal cancer. Two studies (Parent et al., 2000; Vaughan et al., 1997) considered this confounding variable, and one did not (Gérin et al., 1998). Risk factors for other gastrointestinal cancers are less well defined.

Epidemiologic Studies of Exposure to Organic Solvents and Esophageal Cancer

The risk of esophageal cancer was increased in Danish workers who were biologically monitored for a urinary metabolite of trichloroethylene (standardized incidence ratio [SIR] = 4.2, 95% CI = 1.5–9.2) (Hansen et al., 2001). There was no gradient in risk with cumulative exposure although fairly high relative risks were found for long duration of employment (SIR = 6.6, 95% CI = 1.8–17). An equivalent risk estimate and 95% CI were also found among workers with high cumulative exposure. Blair and colleagues (1998) reported an excess risk of esophageal cancer mortality among white male aircraft-maintenance workers exposed to trichloroethylene (SMR = 5.6, 95% CI = 0.7–44.5). In a cohort of aircraft-manufacturing workers in California, Boice and colleagues (1999) found no association between esophageal cancer and potential exposure to trichloroethylene (SMR = 0.83, 95% CI = 0.34–1.72).

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TABLE 6.6 Description of Case–Control Studies of Gastrointestinal Tract Tumors and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Canadian studies							
Gérin et al., 1998	Male cases and controls, age 35–70 years, diagnosed in 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed for one of 19 anatomic cancer sites; frequency matched by approximate age, population-based controls were also chosen from electoral lists and with random-digit dialing (see also Dumas et al., 2000; Goldberg et al., 2001; Parent et al., 2000) Response rates: 82% of all cases, 71% of population controls	99 esophageal 251 stomach 497 colon 257 rectal 116 pancreas	1,066 subjects for each site, consisting of 533 population controls and 533 randomly selected subjects from the eligible cancer control group	Benzene Toluene Xylene	In-person interviews with specific questions on details of each job subject had; analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures) on semiquantitative scales	Unconditional logistic regression	Age, family income, ethnicity, cigarette smoking, respondent status
Dumas et al., 2000	Same as above (see also Gérin et al., 1998; Goldberg et al., 2001; Parent et al., 2000) Response rates: 84.5% of cases, 72% of population controls	257 rectal	1,295 cancer 533 population	Toluene Xylene Methylene chloride Trichloro-ethylene Acetone	See above	See above	Age, education, respondent status, cigarette smoking, beer consumption, body mass index
Parent et al., 2000	Same as above (see also Dumas et al., 2000; Gérin et al., 1998; Goldberg et al., 2001) Response rates: 75% of cases, 71% of population controls	99 esophageal	2,299 cancer 533 population	Toluene Solvents	See above	See above	Age, respondent status, birthplace, educational level, beer consumption, spirits consumption, β–carotene index, cigarette smoking (length and pattern)
Goldberg et al., 2001	Same as above (see also Dumas et al., 2000; Gérin et al., 1998; Parent et al., 2000) Response rates: 82% of cases, 72% of population controls	497 colon	1,514 cancer 533 population	Benzene Xylene Toluene	See above	See above	Age, respondent status, ethnicity, nonoccupational factors (such as cigarette smoking, alcohol consumption)

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
US studies							
Vaughan et al., 1997	Cases, age 20–74 years when diagnosed, identified from a cancer-surveillance system covering 13 counties in western Washington; cases lived in one of the three largest counties and were diagnosed in 1983–1990; population-based controls, frequency-matched by age and sex, identified through RDD Response rates: 82.9 % of cases, 80.3% of controls	404 esophageal and gastric cardia	724	Tetrachloro-ethylene Dry-cleaning work	In-person interviews on occupational history (job titles; including duration, exposure probability, cumulative exposure calculations)	Conditional logistic regression	Age, sex, education, study period, alcohol consumption, cigarette smoking, race
Paulu et al., 1999	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from the records of HCFA and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 79% of cases, 76% of HCFA controls, 74% of RDD controls, 79% of next of kin of deceased controls	311 colon–rectum 36 pancreas	1,158 (colon-rectum) 622 (pancreas)	Tetrachloro-ethylene	Calculated relative delivered dose accounting for location and years of residence, water flow, pipe characteristics	Multiple logistic regression	Age at diagnosis, vital status, sex, occupational exposure to solvents; specific cancer risk factors controlled in respective analyses
European studies							
Fredriksson et al., 1989	Cases age 30–75 years identified through the Swedish Cancer Registry among patients diagnosed in 1980–1983; cases residents of the Umea region and alive during the study's data collection; randomly selected population controls from the National Population Register were frequency-matched on age and sex	329 colon	658	Trichloro-ethylene Organic solvents Dry-cleaning work Painter	Mailed questionnaire assessing occupational history (job titles); telephone interviews followed if necessary; solvent exposures independently coded by two physicians and one hygienist	Mantel-Haenszel	Age, sex, physical activity
Kauppinen et al., 1995	Deceased cases as of April 1990, age 40–74 years at diagnosis in 1984–1987; identified cases and controls from the Finnish Cancer Registry; controls of similar age and period of diagnosis selected from deceased cases of stomach, colon, or rectal cancer Response rates: 47% of cases, 50% of controls	595 pancreatic	1,622	Solvents	Mailed questionnaire to next of kin assessing lifetime work history (job titles); assignment of exposures by industrial hygienist and use of a job–exposure matrix	Unconditional logistic regression	Age, sex, tobacco smoking, diabetes mellitus, alcohol consumption

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Ekstrom et al., 1999	Cases, age 40–79 years, residing in one of the five counties, born in Sweden, and diagnosed in 1989–1995, identified and histologically confirmed by participating clinicians from all hospitals in the study area; control subjects randomly selected from the population register Response rates: 62.4% of cases, 75.9% of controls	565 gastric	1,164	Organic solvents	In-person interview with professional interviewer; occupational epidemiologists to assess type of exposure and duration from self-reports of exposure and job titles	Unconditional logistic regression	Age, sex
Kaerlev et al., 2000	Cases, age 35–69 years, in 10 European countries in 1995–1997 identified from hospital and pathology departments and regional and national cancer registers and histologically confirmed; population-based controls randomly selected from each study base except in Spain, where hospital-based colon cancer cases were used as controls Response rates: 74% of cases, 64% of controls	79 small bowel adeno-carcinoma	579 colon cancer 2070 population	Dry-cleaning work	Standard questionnaire administered in person or over the telephone to determine occupational exposures (job or industry titles, specific work tasks), lifestyle factors; occupation and industry codes used to categorize exposure	Unconditional logistic regression	Sex, country, year of birth
Chinese study Ji et al., 1999	Cases, age 30–74 years, identified through the Shanghai Cancer Registry among patients to diagnosed from October 1990 to June 1993; cases confirmed through histopathology, gross pathology, or tomography; randomly selected population controls from Shanghai were frequency matched on age and sex Response rates: 78.2% of cases, 84.5% of controls	451 pancreatic	1,552	Chemical and rubber work Rubber work Printing	In-person interview with professional interviewers to assess occupational history (job titles); job titles coded by the authors using a scheme developed for use in the Third National Census in 1982	Unconditional logistic regression	Age, education, income, cigarette smoking, other occupations

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing.

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Three cohort studies of workers in the dry-cleaning industry and in aircraft manufacture reported positive associations with esophageal cancer. In a cohort of dry-cleaning union members, Ruder and colleagues (2001) observed associations between esophageal cancer and exposure to tetrachloroethylene (SMR = 2.47, 95% CI = 1.35–4.14) and between esophageal cancer and long-term exposure to tetrachloroethylene (SMR = 5.03, 95% CI = 2.41–9.47). The risk of esophageal cancer observed in workers exposed solely to tetrachloroethylene (SMR = 2.65, 95% CI = 0.85–6.20) was similar to the risk observed in workers exposed to tetrachloroethylene and other dry-cleaning solvents (SMR = 2.40, 95% CI = 1.10–4.56). Blair and colleagues (1990) found an increased risk of esophageal cancer (SMR = 2.1, 95% CI = 1.1–3.6) in another cohort of dry-cleaning union workers; the risk among those with high exposure to dry-cleaning solvents was slightly higher (SRR = 1.3) than the risk in the referent group with medium exposure. An increased risk associated with potential exposure to tetrachloroethylene was found in a cohort of aircraft-manufacturing workers (SMR = 1.47, 95% CI = 0.54–3.21) (Boice et al., 1999). However, no exposure–response pattern was apparent.

Vaughan and colleagues (1997) identified cases of several types of cancer, including two morphologic types of esophageal cancer, in examining the risks from occupational exposure. The risk of esophageal squamous cell carcinoma was increased for possible exposure to tetrachloroethylene (OR = 3.6, 95% CI = 0.5–27.0) and probable exposure (OR = 6.4, 95% CI = 0.6–68.9). Increases in risk of esophageal adenocarcinoma were found to be associated with possible exposure to tetrachloroethylene but not with probable exposure.

Gérin and colleagues (1998) reported no association between medium or high exposure to benzene and risk of esophageal cancer (OR = 0.9, 95% CI = 0.3–2.4). In the large cohort of Chinese benzene-exposed factory workers, increased rates of mortality from esophageal cancer were found (RR = 1.8, 95% CI = 0.8–4.5) (Yin et al., 1996a). The cohort was examined further, including information on cumulative exposure to benzene (Hayes et al., 1996). However, when the cumulative exposure data were categorized, the relative risks did not increase with increasing exposure. The analyses did not adjust for alcohol use, an important risk factor for esophageal cancer and a potential confounder.

Gérin and colleagues (1998) found an increased risk of esophageal cancer with exposure to xylene (OR = 1.4, 95% CI = 0.5–3.8) or toluene (OR = 1.9, 95% CI = 0.9–4.2) in the medium or high exposure category. The risk estimates in the low exposure category for those substances were around unity. In a more comprehensive analysis of the same study, Parent and colleagues (2000) found a similar risk associated with "substantial" exposure to toluene (OR = 1.5, 95% CI = 0.6–3.7). The risk was further increased when the analysis was restricted to cases with squamous cell carcinoma (OR = 2.4, 95% CI = 0.9–6.4).

The only study of methylene chloride was the comprehensive cohort study of Kodak employees (Hearne and Pifer, 1999; Hearne et al., 1987, 1990). The most recent followup of the cohort included two cases of esophageal cancer in the group exposed to methylene chloride and no excess risk was observed.

A cohort study of workers in US chemical plants evaluated the association between exposure to phenol and esophageal cancer risk (Dosemeci et al., 1991). Although a slightly increased risk was associated with "any" exposure to phenol (SMR = 1.6, 95% CI = 0.9–2.6), other studies of unspecified mixtures of solvents yielded no increased risks of esophageal cancer (Anttila et al., 1995: SIR = 0.41, 95% CI = 0.01–2.29; Garabrant et al., 1988: SIR = 1.14, 95% CI = 0.62–1.92; Parent et al., 2000: OR = 1.1, 95% CI = 0.7–1.7).

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Summary and Conclusion

Although almost all the studies of esophageal cancer and exposure to tetrachloroethylene and dry-cleaning solvents showed positive associations, the small number of studies (four) and the lack of increased risk with increased exposure led some committee members to favor the inadequate/insufficient category of association. In addition, some committee members expressed concern over the lack of control or adjustment for tobacco and alcohol use (known risk factors for esophageal cancer) (see Chapter 2 and Appendix E for information on smoking as a potential confounder), whereas others believed that the lack of increased risk of lung and bladder cancer in the same studies constituted evidence that confounding alone could not account for the observed increase in esophageal cancer. As a result, several committee members believed that the evidence was inadequate/insufficient to determine whether an association exists between esophageal cancer and exposure to tetrachloroethylene or dry-cleaning solvents, and others felt that the evidence was limited/suggestive of an association. After extensive discussion and deliberation, the committee decided that it could not reach a consensus on the association. Future committees may re-examine this literature and any new studies that are conducted in the interim to clarify the association between exposure to tetrachloroethylene or dry-cleaning solvents and the risk of esophageal cancer.

In cohort studies of workers exposed to trichloroethylene, most risk estimates for esophageal cancer were increased but highly variable (because there were few exposed subjects), and the estimates of risk were not adjusted for known risk factors, including alcohol consumption. For exposure to benzene, xylene, toluene, methylene chloride, phenol, and solvent mixtures, some of the studies provided positive findings while others did not. Most were not statistically precise. The key studies reviewed by the committee on esophageal cancer are identified in Table 6.7. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than tetrachloroethylene and dry-cleanings solvents, and esophageal cancer.

TABLE 6.7 Selected Epidemiologic Studies—Esophageal Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Any exposure	6	4.2 (1.5–9.2)
	>75 months	4	6.6 (1.8–17)
	Low cumulative exposure	3	6.5 (1.3–19)
	High cumulative exposure	3	4.2 (1.5–9.2)
	Low mean exposure	5	8.0 (2.6–19)
	High mean exposure	1	1.3 (0.02–7.0)
	Low employment duration	2	4.4 (0.5–16)
	High employment duration	4	6.6 (1.8–17)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	7	0.83 (0.34–1.72)
Blair et al., 1998	Aircraft-maintenance workers in Utah, ever exposed	10	5.6 (0.7–44.5)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	Dry-cleaning union workers	14	2.47 (1.35–4.14)
	Long-term exposure[a]	10	5.03 (2.41–9.47)
	Tetrachloroethylene-only	5	2.65 (0.85–6.20)
	Tetrachloroethylene-plus other solvents	9	2.40 (1.10–4.56)
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Potential routine exposure	6	1.47 (0.54–3.21)
	≥5 years routine or intermittent	3	0.91 (0.13–1.60)
Blair et al., 1990	Dry-cleaning union members in St. Louis, MO		
	Dry-cleaning solvents	13	2.1 (1.1–3.6)[b]
	Medium exposure (white males)	1	2.9 (0.1–18.6)[b]
	Medium exposure (black males)	7	3.6 (1.5–7.6)[b]
	High exposure (white males)	0	—
	High exposure (black males)	1	2.0 (0.1–11.1)[b]
Case–Control Study			
Vaughan et al., 1997	Cases from the dry-cleaning industry		
	Squamous cell (possible exposure)	2	3.6 (0.5–27.0)
	Squamous cell (probable)	2	6.4 (0.6–68.9)
	Adenocarcinoma (possible)	2	1.1 (0.2–5.7)
	Adenocarcinoma (probable)	1	0.9 (0.1–10.0)
Benzene			
Cohort Studies—Mortality			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Medium or high exposure	5	0.9 (0.3–2.4)
Yin et al., 1996a	Chinese factory workers ever exposed to benzene	27	1.8 (0.8–4.5)
	Males	25	2.0 (0.9–5.4)
	Females	2	0.8 (0.1–16.7)
Hayes et al., 1996	Chinese factory workers (cumulative exposure to benzene)		
	None	7	1.0
	<10 ppm-years	5	3.5
	10–39 ppm-years	1	0.5
	40–99 ppm-years	3	1.3
	100–400 ppm-years	5	1.1
	>400 ppm-years	13	3.2
			p-trend = 0.09
Xylene and Toluene			
Case–Control Studies			
Parent et al., 2000	Male residents of Montreal, Canada		
	Esophageal		
	Any toluene	16	1.2 (0.7–2.2)
	Substantial toluene	7	1.5 (0.6–3.7)
	Squamous cell		
	Any toluene	15	2.0 (1.0–3.9)
	Substantial toluene	6	2.4 (0.9–6.4)
Gérin et al., 1998	Male residents of Montreal, Canada		
	Medium or high exposure, xylene	5	1.4 (0.5–3.8)
	Medium or high exposure, toluene	9	1.9 (0.9–4.2)
Methylene Chloride			
Cohort Study—Mortality			
Hearne and Pifer, 1999	Male Kodak workers in New York state, employed >1 year		
	Methylene chloride cohort	2	0.63 (0.07–2.28)
	Roll-coating division (external control)	4	1.42 (0.38–3.65)
	Roll-coating division (internal control)	4	1.40 (0.38–3.58)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Phenol			
Cohort Study—Mortality			
Dosemeci et al., 1991	Male workers in five US chemical plants		
	Any exposure	15	1.6 (0.9–2.6)
	No exposure	4	1.0
	Low exposure	11	0.9
	Medium exposure	10	2.3
	High exposure	1	1.1
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	1	0.41 (0.01–2.29)
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years	14	1.14 (0.62–1.92)
Case–Control Study			
Parent et al., 2000	Male residents of Montreal, Canada		
	Esophageal	39	1.1 (0.7–1.7)
	Squamous cell	30	1.4 (0.8–2.5)

[a]Long-term exposure designates 5 years or more of exposure with at least 20 years of latency time.
[b]95% CI calculated by the committee with standard methods from the observed and expected numbers presented iu the original study.

Epidemiologic Studies of Exposure to Organic Solvents and Stomach Cancer

The risk of stomach cancer was not increased in a cohort of Danish workers biologically monitored for a metabolite of trichloroethylene (Hansen et al., 2001). Another Scandinavian cohort, also of workers biologically monitored for trichloroethylene metabolites, showed an increased risk of stomach cancer (SIR = 1.28, 95% CI = 0.75–2.04), but higher concentrations of the metabolite were not associated with greater risks (Anttila et al., 1995). Blair and colleagues (1998) reported increased stomach cancer incidence with exposure greater than 5 years (SIR = 3.1, 95% CI = 0.8–12.1 for 5–25 unit-years of exposure), but the risks did not increase with increasing unit-years of exposure. No increased risk of stomach cancer mortality was reported in the study (SMR = 0.9, 95% CI = 0.4–1.9). A cohort study of aircraft-manufacturing workers in California had increased mortality (SMR = 1.32, 95% CI = 0.77–2.12), but an exposure–response analysis was not presented (Boice et al., 1999). A nested case–control study of rubber workers in Ohio showed no increased risks (Wilcosky et al., 1984).

Two cohort studies of workers in the dry-cleaning industry suggested no association between occupational dry-cleaning solvent exposure and stomach cancer (Blair et al., 1990; Ruder et al., 1994). Boice and co-workers (1999) found an increased risk of stomach cancer in the California cohort of aircraft- manufacturing workers (SMR = 1.42, 95% CI = 0.57–2.93).

No associations were found in the large cohort of Chinese benzene-exposed workers (Hayes et al., 1996; Yin et al., 1996b). In the Montreal case–control study (Gérin et al., 1998), the risk of stomach cancer was associated with medium exposure to benzene (OR = 1.5, 95% CI = 0.8–3.2) and high exposure (OR = 1.3, 95% CI = 0.5–3.2). A slightly increased risk was seen in rubber workers potentially exposed to benzene (Wilcosky et al., 1984).

In a cohort study of rotogravure workers exposed primarily to toluene, Svensson and colleagues (1990) reported an increased risk of stomach cancer mortality (SMR = 2.72, 95% CI

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= 1.09–5.61). Similar risk estimates were reported among subjects with 5 years of exposure or more and at least a 10-year latency period. The cancer incidence results were similar. In the Montreal case–control study (Gérin et al., 1998), the risk of stomach cancer was increased with high exposure to toluene (OR = 1.7, 95% CI = 0.6–4.8), and a similar risk estimate was reported for exposure to xylene (OR = 1.8, 95% CI = 0.3–9.5).

In the Finnish study of workers biologically monitored for aromatic hydrocarbon exposures (xylene, toluene, and styrene), Anttila and colleagues (1998) found increased stomach cancer incidence (SIR = 1.18, 95% CI = 0.54–2.23). In a study of rubber workers potentially exposed to xylene or toluene, no excess risks of stomach cancer were found (Wilcosky et al., 1984).

Two cohort studies of workers exposed to methylene chloride found no persuasive evidence of associations between stomach cancer and exposure (Hearne and Pifer, 1999; Tomenson et al., 1997). Stomach cancer risk was somewhat increased in the Kodak cohort (Hearne and Pifer, 1999), but Tomenson and co-workers (1997) found no association in the cohort of cellulose triacetate workers they followed.

Dosemeci and colleagues (1991) examined stomach cancer associated with exposure to phenol in a cohort of workers at five US chemical plants. No increased risk was found to be associated with "any" exposure (SMR = 0.8, 95% CI = 0.5–1.3) or with categories of increasing exposure. The case–control study conducted among rubber workers included results for several specific solvents (naphthas, ethanol, acetone, isopropanol, and toluene mixture) and stomach cancer risk (Table 6.8). Risk was slightly increased with some exposures but not others (Wilcosky et al., 1984).

In several cohort studies (Acquavella et al., 1993; Anttila et al., 1995; Berlin et al., 1995; Costantini et al., 1989; Fu et al., 1996; Garabrant et al., 1988) and one case–control study (Ekstrom et al., 1999), the association between stomach cancer and exposure to mixed solvents was examined. Except for the Florence cohort of shoemakers (Fu et al., 1996), the studies showed no association with stomach cancer risk. Fu and colleagues (1996) reported a 92% excess risk of stomach cancer associated with solvents used by shoemakers.

Summary and Conclusion

With only one study showing a highly variable positive association, the committee concluded that the data were insufficient to determine whether an association exists between the risk of stomach cancer and exposure to trichloroethylene. For exposure to tetrachloroethylene and dry-cleaning solvents, benzene, xylene, toluene, methylene chloride, phenol, other specific solvents, and solvent mixtures, the results were mixed. Table 6.8 identifies the data points considered by the committee in making its conclusion regarding association for stomach cancer. Unless indicated in the table, the populations cited include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and stomach cancer.

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TABLE 6.8 Selected Epidemiologic Studies—Stomach Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers	3	0.8 (0.2–2.3)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No trichloroethylene exposure	6	1.5 (0.4–6.0)
	<5 unit-years	1	0.3 (0.1–2.6)
	5–25 unit-years	7	3.1 (0.8–12.1)
	>25 unit-years	6	2.0 (0.5–8.1)
Anttila et al., 1995	Finnish workers biologically monitored for exposure		
	Years since first measurement		
	0–9 years	6	1.32 (0.48–2.87)
	10–19 years	4	0.63 (0.17–1.60)
	20+ years	7	2.98 (1.20–6.13)
	Whole period	17	1.28 (0.75–2.04)
	Mean personal U-TCA level		
	<100 µmol/L	12	1.65 (0.98–1.39)
	100+ µmol/L	4	0.91 (0.25–2.32)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	17	1.32 (0.77–2.12)
Blair et al., 1998	Aircraft-maintenance workers in Utah, employed >1 year	23	0.9 (0.4–1.9)
Wilcosky et al., 1984	Male rubber workers in Ohio, exposed >1 year	5	1.0
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	7	1.42 (0.57–2.93)
Ruder et al., 1994	Dry-cleaning labor-union workers	5	0.61 (0.20–1.43)
	Males	2	0.43 (0.05–1.54)
	Females	3	0.86 (0.18–2.53)
Blair et al., 1990	Dry-cleaning union members in St. Louis, MO		
	Dry-cleaning solvents	11	0.8 (0.4–1.4)
Benzene			
Cohort Studies—Incidence			
Yin et al., 1996a	Chinese factory workers ever exposed to benzene	85	0.9 (0.7–1.4)
	Males	71	0.9 (0.6–1.4)
	Females	14	1.0 (0.4–2.8)
Hayes et al., 1996	Chinese factory workers (cumulative exposure to benzene)		
	None	43	1.0
	<10 ppm-years	6	0.6
	10–39 ppm-years	13	1.0
	40–99 ppm-years	12	0.9
	100–400 ppm-years	25	1.0
	400+ ppm-years	27	1.2
			p-trend = 0.63
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Benzene, medium exposure	11	1.5 (0.8–3.2)
	Benzene, high exposure	6	1.3 (0.5–3.2)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Xylene and Toluene			
Cohort Studies—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons (styrene, toluene, xylene)	9	1.18 (0.54–2.23)
Svensson et al., 1990	Male rotogravure workers in Sweden	7	2.34 (0.94–4.82)
	≥5 years exposure with ≥10 years latency (primarily to toluene)	5	2.18 (0.71–5.09)
Cohort Studies—Mortality			
Svensson et al., 1990	Male rotogravure workers in Sweden	7	2.72 (1.09–5.61)
	≥5 years exposure with ≥10 years latency (primarily to toluene)	5	2.53 (0.82–5.91)
Wilcosky et al., 1984	Male rubber workers in Ohio, exposed >1 year		
	Xylenes	3	0.53
	Toluene	1	—
	Benzene	12	1.3
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Xylene, medium exposure	7	1.0 (0.4–2.3)
	Xylene, high exposure	2	1.8 (0.3–9.5)
	Toluene, medium exposure	7	1.0 (0.4–2.2)
	Toluene, high exposure	5	1.7 (0.6–4.8)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne and Pifer, 1999	Male Kodak workers in New York state, employed >1 year		
	Methylene chloride cohort	6	1.40 (0.51–3.04)
	Roll-coating division (external control)	5	1.25 (0.40–2.91)
	Roll-coating division (internal control)	5	1.26 (0.41–2.93)
Tomenson et al., 1997	Male cellulose triacetate film workers in Brantham, UK, ever employed	6	0.63 (0.23–1.37)
Other Organic Solvents			
Cohort Studies—Mortality			
Dosemeci et al., 1991	Male workers in five US chemical plants		
	Phenol		
	No exposure	10	1.1
	Any exposure	18	0.8 (0.5–1.3)
	Low exposure	11	1.0
	Medium exposure	5	0.5
	High exposure	2	1.1
Wilcosky et al., 1984	Male rubber workers in Ohio, exposed >1 year		
	Specialty naphthas	18	1.1
	Ethanol	8	1.1
	Acetone	1	—
	Isopropanol	14	1.4
	Phenol	6	1.4
	VM&P naphtha	3	1.1
	Solvent “A” (toluene mixture)	15	1.4
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	19	1.28 (0.77–1.99)
Berlin et al., 1995	Swedish patients with acute solvent-related disorders	2	0.5 (0.1–1.9)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Cohort Studies—Mortality			
Fu et al., 1996	Shoemakers in England and Florence		
	English cohort		
	Probable solvents	29	0.88 (0.59–1.27)
	High solvent	5	1.72 (0.56–4.02)
			1.92 (1.02–3.29)
	Florence cohort		1.93 (1.00–3.36)
	Probable solvents	13	
	High solvent	12	
Acquavella et al., 1993	Metal-components manufacturing workers		
	Solvents, ever exposed	0	0.0 (0.0–17.6)
Costantini et al., 1989	Male leather workers in Tuscany, Italy, employed >6 months	6	0.43 (0.16–0.94)
Garabrant et al., 1988	Aircraft manufacturing workers in California, employed >4 months	9	0.40 (0.18–0.76)
Case–Control Study			
Ekstrom et al., 1999	Residents of two regions in Sweden		
	Organic solvents, ever exposed	232	1.08 (0.87–1.33)

NOTE: U-TCA = urinary metabolite of trichloroethylene.

Epidemiologic Studies of Exposure to Organic Solvents and Colon Cancer

In a study conducted in Sweden (Fredriksson et al., 1989), a 640% excess risk of colon cancer (OR = 7.4, 95% CI = 1.1–47.0) was found with exposure to trichloroethylene among dry cleaners. Two cohort studies of aircraft workers did not show increased mortality from colon cancer (Blair et al., 1998; Boice et al., 1999). However, the incidence of colon cancer was increased in the cohort of aircraft-maintenance workers in Utah (Blair et al., 1998). Incidence increased with increasing unit-years of exposure (Table 6.9). Colon cancer risk was not increased in two cohorts biologically monitored for exposure to trichloroethylene (Anttila et al., 1995; Hansen et al., 2001). Anttila and co-workers found no increased risk associated with number of years since first measurement, which represents an approach to account for latency.

A case–control study of colon cancer in Sweden conducted by Fredriksson and colleagues (1989) reported an increased risk of colon cancer among female dry cleaners (OR = 2.0, 95% CI = 0.5–7.1). Paulu and colleagues (1999) conducted a case–control study of residents of Cape Cod that showed an increased risk of colorectal cancers with tetrachloroethylene exposure in drinking water ($OR_{11\ year\ latency}$ = 2.0, 95% CI = 0.6–5.8) for exposures less than the 50th percentile, whereas the risk was somewhat lower when exposure equal to or greater than the 50th percentile was considered ($OR_{11\ year\ latency}$ = 1.5, 95% CI = 0.4–4.4). A cohort of dry-cleaning workers experienced an increased risk of intestinal (excluding rectal) cancer (SMR = 1.48, 95% CI = 1.01–2.09), and findings were similar in a subcohort exposed to both tetrachloroethylene and other solvents; however, the risk was not similarly increased among those exposed only to tetrachloroethylene (Ruder et al., 2001). Because the analysis was based on cases of "intestinal" cancer, the findings are difficult to interpret; different classes of intestinal tract cancers, including cancers of the small and large intestines, are derived from distinct cells and may have different etiology. Real effects may be masked when diseases with different

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etiology are investigated as one disease. Furthermore, when exposure was restricted to tetrachloroethylene, no increase risk was apparent.

Goldberg and colleagues (2001) reported an increased colon cancer risk with exposure to benzene at "substantial," "medium," and "high" levels; and risks increased by about 10% for every 10 years of exposure. In the large cohort of Chinese benzene-exposed workers, no increased risks of colorectal cancer were found (RR = 0.9, 95% CI = 0.5–1.7) (Yin et al., 1996a). Increasing cumulative exposure did not appear to be associated with increased risk (Hayes et al., 1996).

In detailed followup analyses of the population-based case–control study of occupational exposure and cancer in Montreal, the risk of colon cancer was increased with "substantial" exposure to xylene (OR = 1.5, 95% CI = 0.6–3.7) and toluene (OR = 1.5, 95% CI = 0.8–2.5) (Goldberg et al., 2001). Risk estimates increased with increasing concentration of xylene and toluene, and risk increased by 20% for every 10 years of exposure. Levels were assessed on the basis of responses to interviews and structured questionnaires that were coded by a team of chemists and industrial hygienists. Low levels were assumed if a person had been exposed peripherally or at normal levels, and high levels were assumed if a person directly handled a product that contained one of the chemicals of concern. Medium concentration fell between those two.

Colon cancer risk was not increased among workers monitored for hydrocarbons, which included styrene, toluene, and xylene (Anttila et al., 1998). In a cohort study of cancer incidence and mortality in toluene-exposed rotogravure workers, Svensson and colleagues (1990) reported an increased risk of combined colon and rectal cancer mortality (SMR = 2.18, 95% CI = 0.88–4.49) and incidence (SIR = 1.49, 95% CI = 0.68–2.84). Similar risk estimates were reported among subjects with prolonged exposure.

Two cohort studies of workers exposed to methylene chloride reported no increased colon cancer risk in the roll-coating division at Kodak (Hearne and Pifer, 1999) or in cellulose triacetate film workers in the UK (Tomenson et al., 1997). The committee concluded that these results did not indicate excess risk of colon cancer posed by exposure to methylene chloride.

One study reported no increased colon cancer risk associated with exposure to phenol (Dosemeci et al., 1991). Risk of colon cancer was not associated with exposure to solvents in a cohort of patients with solvent-related disorders (Berlin et al., 1995) or among workers biologically monitored for halogenated hydrocarbons (Anttila et al., 1995). Self-reported occupation as a painter and occupational exposure to solvents were each associated with colon cancer in a study conducted in Sweden (Fredriksson et al., 1989).

Summary and Conclusion

Because the increased risk and exposure–response pattern support an association between colon cancer and exposure to trichloroethylene, several committee members believed that the evidence was limited/suggestive of an association. Other members felt that the positive associations were balanced by the negative findings in other cohort studies and in studies with biologic monitoring of metabolites of exposure. Therefore, the committee decided not to have a consensus conclusion. Additional research will help to clarify the relationship between exposure to trichloroethylene and the risk of colon cancer.

Results of the three studies on tetrachloroethylene and dry-cleaning solvents are insufficient to determine whether an association exists for colon cancer, because of the described

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limitations of the cohort study and because the estimates of risk in the case–control studies are imprecise, being based on few exposed cases.

The body of evidence on colon cancer and exposure to benzene and mixtures of toluene and xylene was rather small (five studies), including one high quality case–control study (Goldberg et al., 2001) and two cohort studies that included exposures other than benzene, toluene, or xylene in their analyses (Anttila et al., 1998; Svensson et al., 1990). Anttila and colleagues (1998) assessed the association between colon cancer and hydrocarbons that included styrene in addition to toluene and xylene; and Svensson and colleagues (1990), who examined a cohort of Swedish rotogravure printers, focused primarily on toluene but acknowledged the presence of other solvents and chemical agents. Although one study showed an association with exposure to benzene, toluene, and xylene (Goldberg et al., 2001), the large Chinese factory-worker study (Hayes et al., 1996; Yin et al., 1996b), which combined colon and rectal cancer, did not. The strengths of the Goldberg and colleagues study (2001) included adjustment for most known risk factors and occupational exposures; use of incident, histologically-confirmed cases; and an independent assessment of exposure by experts. The strength of the Chinese cohort study (Hayes et al., 1996) was the relatively accurate estimates of exposure, but its limitations included use of mortality instead of incidence and lack of assessment of confounding factors. As a result, some committee members concluded that the evidence was limited/suggestive of an association, and others concluded that it was insufficient to determine whether an association exists. After much deliberation, the committee decided that it could not reach a consensus on an association of colon cancer and exposure to benzene and mixtures of toluene and xylene. Further studies on these exposure–outcome relationships may provide evidence as to whether an association exists.

For exposure to methylene chloride, phenol, and mixtures of solvents, the studies did not provide any evidence of an association between exposure and risk for colon cancer. All of the studies reviewed by the committee are identified below in Table 6.9, and unless indicated, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than trichloroethylene, benzene, toluene, and xylene, and colon cancer.

TABLE 6.9 Selected Epidemiologic Studies—Colon Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males	5	0.7 (0.2–1.6)
	Females	1	0.7 (0.01–4.0)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No trichloroethylene exposure	22	4.1 (1.4–11.8)
	≤5 unit-years	15	2.9 (1.0–8.9)
	5–25 unit-years	14	4.3 (1.4–13.0)
	>25 unit-years	23	5.7 (2.0–16.7)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Anttila et al., 1995	Biologically monitored Finnish workers		
	Years since first measurement:		
	0–9 years	3	1.23 (0.25–3.59)
	10–19 years	3	0.62 (0.13–1.80)
	20+ years	2	0.92 (0.11–3.31)
	Whole period	8	0.84 (0.36–1.66)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	30	1.07 (0.72–1.52)
Blair et al., 1998	Aircraft-maintenance workers in Utah	54	1.4 (0.8–2.4)
	Males		
	No trichloroethylene exposure	21	1.5 (0.7–3.3)
	<5 unit-years	19	1.5 (0.7–3.3)
	5–25 unit-years	12	1.5 (0.7–3.6)
	>25 unit-years	15	1.5 (0.7–3.3)
Case–Control Study			
Fredriksson et al., 1989	Residents of Sweden		
	Trichloroethylene	NA	1.5 (0.4–5.7)
	Trichloroethylene among dry cleaners	NA	7.4 (1.1–47.0)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Mortality			
Ruder et al., 2001	Dry-cleaning labor-union workers (intestine)	32	1.48 (1.01–2.09)
	Long-term exposure[a]	13	1.48 (0.79–2.58)
	Tetrachloroethylene only	8	1.18 (0.51–2.33)
Case–Control Studies			
Paulu et al., 1999	Residents of Cape Cod, MA		
	Colon–rectum (11-year latency)		
	≤Median	6	2.0 (0.6–5.8)
	>Median	5	1.5 (0.4–4.4)
Fredriksson et al., 1989	Residents of Sweden		
	Female dry cleaners	5	2.0 (0.5–7.1)
Benzene			
Cohort Studies—Mortality			
Yin et al., 1996a	Chinese factory workers ever exposed to benzene (colon–rectum)		
	Total	34	0.9 (0.5–1.7)
	Males	24	1.1 (0.5–2.3)
	Females	10	0.7 (0.3–2.0)
Hayes et al., 1996	Chinese factory workers (colorectal; benzene cumulative exposure)		
	None	17	1.0
	<10 ppm-years	7	1.5
	10–39 ppm-years	4	0.7
	40–99 ppm-years	3	0.5
	100–400 ppm-years	8	0.8
	400+ ppm-years	12	1.4
			p-trend = 0.91

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Study			
Goldberg et al., 2001	Male residents of Montreal, Canada		
	Substantial exposure	21	1.6 (0.9–2.8)
	Low concentration	39	0.8 (0.5–1.2)
	Medium concentration	26	1.5 (0.9–2.4)
	High concentration	6	3.4 (1.0–11.2)
	Duration (10 years)	71	1.1 (0.9–1.2)
Xylene and Toluene			
Cohort Studies—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons (styrene, toluene, and xylene)	2	0.34 (0.04–1.21)
Svensson et al., 1990	Male rotogravure workers in Sweden—colon–rectum	9	1.49 (0.68–2.84)
	≥5 yrs exposure with >10 yrs latency (primarily toluene)	8	1.74 (0.75–3.43)
Cohort Study—Mortality			
Svensson et al., 1990	Male rotogravure workers in Sweden—colon–rectum	7	2.18 (0.88–4.49)
	≥5 yrs exposure with >10 yrs latency (primarily to toluene)	6	2.41 (0.89–5.25)
Case–Control Study			
Goldberg et al., 2001	Male residents of Montreal, Canada		
	Xylene		
	Substantial exposure	10	1.5 (0.6–3.7)
	Low concentration	44	1.4 (0.9–2.0)
	Medium concentration	11	1.7 (0.8–3.5)
	High concentration	5	4.0 (1.1–15.1)
	Duration (10 years)	60	1.2 (1.0–1.4)
	Toluene		
	Substantial exposure	27	1.5 (0.8–2.5)
	Low concentration	31	1.3 (0.8–2.0)
	Medium concentration	31	1.3 (0.8–2.1)
	High concentration	9	2.4 (1.0–5.7)
	Duration (10 years)	71	1.2 (1.0–1.4)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne and Pifer, 1999	Male Kodak workers in New York state (colon–rectum), employed >1 year		
	Methylene chloride cohort	15	1.15 (0.64–1.90)
	Roll-coating division (external control)	10	0.75 (0.36–1.37)
	Roll-coating division (internal control)	10	0.87 (0.42–1.60)
Tomenson et al., 1997	Male cellulose triacetate film workers in Brantham, UK, ever employed	6	0.90 (0.33–1.96)
Phenol			
Cohort Study—Mortality			
Dosemeci et al., 1991	Male workers in five US chemical plants		
	Phenol, any exposure	33	0.9 (0.6–1.3)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	8	0.74 (0.32–1.44)
Berlin et al., 1995	Swedish patients with acute solvent-related disorders	2	0.6 (0.1–2.2)
Case–Control Study			
Fredriksson et al., 1989	Residents of Sweden		
	Organic solvents		
	High-grade	NA	2.1 (0.8–5.8)
	Low-grade	NA	1.3 (0.8–2.0)
	Painters	7	3.0 (0.9–9.2)

NOTE: NA = not available.
[a]Long-term exposure designates 5 years or more of exposure with at least 20 years of latency.

Epidemiologic Studies of Exposure to Organic Solvents and Rectal Cancer

The two studies of workers biologically monitored for a metabolite of trichloroethylene showed imprecise associations (Anttila et al., 1995; Hansen et al., 2001). Risks did not increase with increasing mean urinary trichloroacetic acid, a metabolite of trichloroethylene (SIR = 0.85, 95% CI = 0.10–3.07) (Anttila et al., 1995).

No associations with rectal cancer mortality were found in the studies of aircraft and aerospace workers. Blair and colleagues (1998) found no increased risk of rectal cancer among aircraft maintenance workers in Utah (SMR = 0.4, 95% CI = 0.1–1.5). Among a trichloroethylene-exposed subcohort of aerospace workers, the SMR for "high" exposure was 1.38 (95% CI = 0.45–3.21) (Morgan et al., 1998). In the cohort of aircraft-manufacturing workers in California, the SMR was 1.29 (95% CI = 0.59–2.45) (Boice et al., 1999). Rectal cancer risk was found to be increased in the Montreal case–control study with "any" exposure to trichloroethylene (OR = 2.0, 95% CI = 1.0–3.9), but it was much lower with "substantial" exposure to trichloroethylene (OR = 0.9, 95% CI = 0.3–3.2) (Dumas et al., 2000).

The cohort of dry-cleaning union members experienced an excess risk of rectal cancer mortality after exposure to tetrachloroethylene and other dry-cleaning solvents (SMR = 2.16, 95% CI = 0.86–4.45) (Ruder et al., 2001). Paulu and colleagues (1999) conducted a case–control study of residents of Cape Cod that showed an increased risk of colorectal cancers with exposure to tetrachloroethylene from drinking water ($OR_{11\ year\ latency}$ = 2.0, 95% CI = 0.6–5.8) when exposure was less than the 50th percentile; the risk was somewhat lower when exposure was equal to or greater than the 50th percentile ($OR_{11\ year\ latency}$ = 1.5, 95% CI = 0.4–4.4). Because the analysis was based on cases of "intestinal" cancer, the findings are difficult to interpret; different classes of intestinal tract cancers, including cancers of the small and large intestines, are derived from different cells and may have different etiology. Real effects may be masked when diseases with different etiology are studied as one disease. No cases were found in workers exposed only to tetrachloroethylene.

In the large cohort of Chinese benzene-exposed workers, no increased risk of colorectal cancer was found (RR = 0.9, 95% CI = 0.5–1.7) (Yin et al., 1996a). Increasing cumulative exposure did not appear to be associated with increased risk (Hayes et al., 1996). Only in the population-based case–control study of occupational exposure and cancer in Montreal was

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exposure to xylene, toluene, and benzene assessed. Gérin and colleagues (1998) found no association with "high" exposure to benzene (OR = 0.8, 95% CI = 0.3–2.5). In additional analyses of the data, Dumas and colleagues (2000) found increased rectal cancer risk with "substantial" exposure to xylene (OR = 2.9, 95% CI = 1.1–7.3) and "substantial" exposure to toluene (OR = 1.7, 95% CI = 1.0–3.0).

In the cohort study of Finnish workers biologically monitored for exposure to solvents, rectal cancer incidence was associated with exposure to styrene, xylene, and toluene (aromatic hydrocarbons) (SIR = 1.88, 95%CI 0.81–3.71) (Anttila et al., 1998).

The cohort study of cellulose triacetate film workers in the UK showed no increased risk of rectal cancer (SMR = 0.44, 95% CI = 0.05–1.57) (Tomenson et al., 1997). Dumas and colleagues (2000) reported an increased risk of rectal cancer with "any" exposure to methylene chloride (OR = 1.2, 95% CI = 0.5–2.8); the risk was higher with "substantial" exposure (OR = 3.8, 95% CI = 1.1–12.9).

The association between rectal cancer and exposure to phenol was assessed in one cohort study (Dosemeci et al., 1991); there was no strong evidence of an association (SMR = 1.4, 95% CI = 0.8–2.2). Dumas and colleagues (2000) found an increased risk with "any" exposure to acetone (OR = 2.3, 95% CI = 1.1–4.7), which increased to an OR of 4.8 (95% CI = 1.8–13.0) with "substantial" exposure.

There were three cohort studies of rectal cancer and exposure to unspecified mixtures of solvents. An early study of aircraft-manufacturing workers (Garabrant et al., 1988) and a study of Swedish patients with solvent-related disorders (Berlin et al., 1995) showed no associations with rectal cancer (SIR = 1.04 and 0.99, respectively). Anttila and colleagues (1995) reported an increased risk of rectal cancer among workers biologically monitored for halogenated hydrocarbon exposure (SIR = 1.63, 95% CI = 0.87–2.78).

Summary and Conclusion

In summary, there was inconclusive evidence of an association between trichloroethylene and rectal cancer. The main limitation of the studies was the small number of exposed cases; this limits the precision of the estimates and the statistical power to detect associations. For exposure to tetrachloroethylene and dry-cleaning solvents, the committee concluded that the results did not indicate an excess risk of rectal cancer. Despite the suggestive findings on toluene and xylene, only two studies specifically examined rectal cancer risk. To determine whether an association exists, other high-quality studies are required.

Because there were only two studies to draw inferences from, the evidence for methylene chloride was inadequate. Furthermore, the committee could not draw conclusions from single studies of each exposure although there was suggestive evidence from the high-quality study of Dumas and colleagues regarding exposure to acetone. For exposure to solvent mixtures, the findings were mixed with no persuasive evidence of an association.

Table 6.10 identifies the studies and data points considered by the committee in making its conclusion regarding association. Unless indicated, the study populations identified in the table include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and rectal cancer.

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TABLE 6.10 Selected Epidemiologic Studies—Rectal Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers	7	1.3 (0.5–2.7)
Anttila et al., 1995	Biologically monitored Finnish workers		
	Entire period since first measurement	12	1.71 (0.88–2.98)
	0–9 years	3	1.59 (0.33–4.64)
	10–19 years	8	2.22 (0.96–4.36)
	20+ years	1	0.67 (0.02–3.72)
	Mean personal U-TCA level:		
	<100 µmol/L	9	2.34 (1.07–4.44)
	100+ µmol/L	2	0.85 (0.10–3.07)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	9	1.29 (0.59–2.45)
Blair et al., 1998	Aircraft-maintenance workers in Utah, employed >1 year	5	0.4 (0.1–1.5)
Morgan et al., 1998	Aerospace workers in Arizona		
	Trichloroethylene-exposed subcohort	6	1.06 (0.39–2.31)
	High trichloroethylene-exposure	5	1.38 (0.45–3.21)
Case–Control Study			
Dumas et al., 2000	Male residents of Montreal, Canada		
	Any exposure	12	2.0 (1.0–3.9)
	Substantial exposure	3	0.9 (0.3–3.2)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Mortality			
Ruder et al., 2001	Dry-cleaning labor-union workers (intestine)		
	Tetrachloroethylene plus other solvents	7	2.16 (0.86–4.45)
Case–Control Study			
Paulu et al., 1999	Residents of Cape Cod, MA		
	Colon–rectum (11-year latency)		
	≤Median	6	2.0 (0.6–5.8)
	>Median	5	1.5 (0.4–4.4)
Benzene			
Cohort Studies—Mortality			
Yin et al., 1996a	Chinese factory workers ever exposed to benzene (colon–rectum)		
	Total	34	0.9 (0.5–1.7)
	Males	24	1.1 (0.5–2.3)
	Females	10	0.7 (0.3–2.0)
Hayes et al., 1996	Chinese factory workers (colorectal; benzene cumulative exposure)		
	None	17	1.0
	<10 ppm-years	7	1.5
	10–39 ppm-years	4	0.7
	40–99 ppm-years	3	0.5
	100–400 ppm-years	8	0.8
	400+ ppm-years	12	1.4
			p-trend = 0.91
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	High exposure	4	0.8 (0.3–2.5)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Xylene and Toluene			
Cohort Study—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons (styrene, toluene, xylene)	8	1.88 (0.81–3.71)
Case–Control Study			
Dumas et al., 2000	Male residents of Montreal, Canada		
	Xylene		
	Any exposure	39	1.3 (0.9–1.9)
	Substantial exposure	7	2.9 (1.1–7.3)
	Toluene		
	Any exposure	50	1.4 (1.0–2.0)
	Substantial exposure	17	1.7 (1.0–3.0)
Methylene Chloride			
Cohort Study—Mortality			
Tomenson et al., 1997	Male cellulose triacetate film workers in Brantham, UK, ever employed	2	0.44 (0.05–1.57)
Case–Control Study			
Dumas et al., 2000	Male residents of Montreal, Canada		
	Any exposure	7	1.2 (0.5–2.8)
	Substantial exposure	5	3.8 (1.1–12.9)
Phenol and Acetone			
Cohort Study—Mortality			
Dosemeci et al., 1991	Male workers in five US chemical plants		
	Phenol		
	No exposure	6	1.1
	Any exposure	18	1.4 (0.8–2.2)
	Low exposure	9	1.4
	Medium exposure	9	1.5
	High exposure	0	0
Case–Control Study			
Dumas et al., 2000	Male residents of Montreal, Canada		
	Acetone		
	Any exposure	11	2.3 (1.1–4.7)
	Substantial exposure	8	4.8 (1.8–13.0)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	13	1.63 (0.87–2.78)
Berlin et al., 1995	Swedish patients with acute solvent-related disorders	2	0.99 (0.1–3.6)
Cohort Study—Mortality			
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years	15	1.04 (0.59–1.73)

NOTE: U-TCA = urinary metabolite of trichloroethylene.

Epidemiologic Studies of Exposure to Organic Solvents and Pancreatic Cancer

Several cohort studies of trichloroethylene-exposed workers showed no increased risk of pancreatic cancer. In the cohort of aircraft-manufacturing workers examined by Boice and

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colleagues (1999), risk was shown to decrease (SMR = 0.41, 95% CI = 0.17–0.85) with potential exposure to trichloroethylene. Blair and co-workers (1998) also found no association between pancreatic cancer incidence and all categories of "unit-years" of exposure. Pancreatic cancer mortality was weakly increased in the same study (SMR = 1.2, 95% CI = 0.6–2.3). A third cohort study of aerospace workers in Arizona also found no risk of pancreatic cancer posed by exposure to high levels of trichloroethylene (SMR = 0.66, 95% CI = 0.24–1.43) (Morgan et al., 1998).

Two cohorts of workers biologically monitored for metabolites of trichloroethylene reported mixed findings. Hansen and colleagues (2001) found no association (SIR = 1.0, 95% CI = 0.2–3.0) between the trichloroethylene metabolite and pancreatic cancer, whereas Anttila and colleagues (1995) found an increased risk (SIR = 1.61, 95% CI = 0.81–2.88). However, no exposure–response relationship was indicated as the mean concentration of the metabolite increased.

Ruder and colleagues (2001) found an association between pancreatic cancer and exposure to tetrachloroethylene and other solvents (SMR = 1.89, 95% CI = 1.06–3.11), but no increase in risk was found in the subcohort of workers exposed only to tetrachloroethylene (SMR = 0.80, 95% CI = 0.17–2.35). An increased risk of pancreatic cancer was found in the cohort of workers monitored for solvents, including tetrachloroethylene (SIR = 3.08, 95% CI = 0.63–8.99) (Anttila et al., 1995).

The case–control study of multiple cancer sites performed by Gérin and colleagues (1998) indicated no association between pancreatic cancer and medium or high exposure to toluene (OR = 0.6, 95% CI = 0.2–2.2), xylene (OR = 1.1, 95% CI = 0.4–3.3), or benzene (OR = 0.4, 95% CI = 0.1–1.4). In the cohort study of Finnish workers exposed to xylene, toluene, and styrene, Anttila and colleagues (1998) found increased risks of pancreatic cancer (SIR = 1.26, 95% CI = 0.41–2.93). A case–control study of pancreatic cancer by Ji and colleagues (1999) conducted in Shanghai showed increased risks in various occupational groups, especially among male painters (OR = 5.2, 95% CI = 1.1–25.0).

The comprehensive cohort study of methylene chloride-exposed workers at Kodak has been followed for a number of years (Hearne et al., 1987, 1990). In the initial publication, an excess of pancreatic cancer was observed (SMR = 3.1); however, in the second study, after 4 additional years of followup, there was no increase in pancreatic cancer mortality. In a study examining the same cohort and another cohort of Kodak workers, Hearne and Pifer (1999) showed an increased risk of pancreatic cancer associated with career exposure to methylene chloride of over 800 ppm-years on the basis of three cases (SMR = 2.34, compared with internal controls). Among workers who were employed in 1964–1970 in the roll coating division, the highest risk was found in the lowest cumulative-exposure category of less than 400 ppm (SMR = 2.58, compared with internal controls). Other cohorts of methylene chloride-exposed workers had very few cases of pancreatic cancer and reported no increased risk (Gibbs et al., 1996; Lanes et al., 1990, 1993; Tomenson et al., 1997).

The study of workers in five chemical plants found no increased risk of pancreatic cancer associated with exposure to phenol (SMR = 0.6, 95% CI = 0.4–1.1) (Dosemeci et al., 1991).

Several studies reported associations between pancreatic cancer and unspecified mixtures of organic solvents (Table 6.11). The studies showing positive associations included male leather workers in Italy (SMR = 1.46, 95% CI = 0.39–3.73) (Costantini et al., 1989), aircraft-manufacturing workers (SMR = 1.19, 95% CI = 0.83–1.67) (Garabrant et al., 1988), and the

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case–control study in Finland of high exposure to solvents (OR = 2.01, 95% CI = 0.98–4.10) (Kauppinen et al., 1995).

Summary and Conclusion

For exposure to trichloroethylene, tetrachloroethylene and dry-cleaning solvents, xylene, toluene, benzene, methylene chloride, phenol, and solvent mixtures and the risk of pancreatic cancer, the evidence was limited by mixed results, the lack of exposure–response relationships, and imprecise estimates of risk. Table 6.11 identifies the studies reviewed by the committee in making its conclusion regarding association. All of the study populations include both men and women unless stated otherwise.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and pancreatic cancer.

TABLE 6.11 Selected Epidemiologic Studies—Pancreatic Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers	3	1.0 (0.2–3.0)
Blair et al., 1998	Aircraft maintenance workers in Utah		
	No trichloroethylene exposure	6	0.7 (0.2–2.3)
	<5 unit-years	6	0.7 (0.2–2.1)
	5–25 unit-years	2	0.4 (0.1–1.8)
	>25 unit-years	51	0.7 (0.2–2.4)
Anttila et al., 1995	Biologically monitored Finnish workers		
	Entire period since first measurement:	11	1.61 (0.81–2.88)
	0–9 years	1	0.56 (0.01–3.10)
	10–19 years	8	2.30 (0.99–4.52)
	20+ years	2	1.31 (0.16–4.74)
	Mean personal U-TCA level:		
	<100 μmol/L	6	1.61 (0.59–3.50)
	100+ μmol/L	3	1.31 (0.27–3.82)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	7	0.41 (0.17–0.85)
Blair et al., 1998	Aircraft-maintenance workers in Utah, employed >1 year	33	1.2 (0.6–2.3)
Morgan et al., 1998	Aerospace workers in Arizona		
	Trichloroethylene-exposed subcohort	11	0.76 (0.38–1.37)
	High trichloroethylene-exposure	6	0.66 (0.24–1.43)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Biologically monitored Finnish workers	3	3.08 (0.63–8.99)
Cohort Study—Mortality			
Ruder et al., 2001	Dry-cleaning labor-union workers	18	1.53 (0.91–2.42)
	Tetrachloroethylene-only	3	0.80 (0.17–2.35)
	Tetrachloroethylene-plus other solvents	15	1.89 (1.06–3.11)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Xylene, Toluene, Benzene			
Cohort Study—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons (styrene, toluene, xylene)	5	1.26 (0.41–2.93)
Case–Control Studies			
Ji et al., 1999	Residents of Shanghai, China		
	Chemical and rubber workers (female)	5	1.4 (0.4–4.7)
	Rubber workers (female)	5	1.7 (0.5–5.8)
	Printers (male)	4	5.2 (1.1–25.0)
Gérin et al., 1998	Male residents of Montreal, Canada		
	Xylene, medium/high exposure	4	1.1 (0.4–3.3)
	Toluene, medium/high exposure	3	0.6 (0.2–2.2)
	Benzene, medium/high exposure	3	0.4 (0.1–1.4)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne and Pifer, 1999	Male Kodak workers in New York state, employed >1 year		
	Methylene chloride cohort	5	0.92 (0.30–2.14)
	Internal comparison, ≥800 ppm-years	3	2.34
	Roll-coating division (New York state control)	8	1.51 (0.65–2.98)
	Roll-coating division (Kodak Rochester control)	8	1.55 (0.67–3.06)
Tomenson et al., 1997	Male cellulose triacetate film workers, ever employed	3	0.68 (0.14–1.99)
Gibbs et al., 1996	Cellulose-fiber production workers		
	High exposure, males	1	0.35 (0.01–1.92)
	High exposure, females	0	0
	Low exposure, males	2	0.89 (0.11–3.22)
	Low exposure, females	1	0.58 (0.01–3.23)
Lanes et al., 1993	Cellulose-fiber production plant workers, employed >3 months	2	0.83 (0.10–2.99)
Phenol			
Cohort Study—Mortality			
Dosemeci et al., 1991	Male workers in five US chemical plants		
	Phenol, any exposure	14	0.6 (0.4–1.1)
Unspecified Mixtures of Organic Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	12	1.56 (0.81–2.72)
Cohort Studies—Mortality			
Fu et al., 1996	Shoemakers in England and Florence		
	English cohort	25	0.70 (0.45–1.04)
	Florence cohort	2	0.54 (0.07–1.95)
Acquavella et al., 1993	Metal-components manufacturing workers, ever exposed	1	2.9 (0.1–16.0)
Costantini et al., 1989	Male leather workers in Tuscany, Italy, employed >6 months	4	1.46 (0.39–3.73)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years	34	1.19 (0.83–1.67)
Pippard and Acheson, 1985	Male boot and shoe makers in three English towns		
	Rushden	21	0.96 (0.59–1.46)
	Street	2	0.40 (0.05–1.46)
	Stafford	6	0.96 (0.35–2.11)
McMichael et al., 1976	Male rubber workers in Ohio and Wisconsin		
	Age 40–64	17	0.95 (0.55–1.52)[a]
	Age 65–84	40	1.08 (0.77–1.47)[a]
	Age 40–84	57	1.03 (0.78–1.33)[a]
Case–Control Study			
Kauppinen et al., 1995	Residents of Finland		
	Solvents (all)	20	1.22 (0.73–2.07)
	Solvents (high)	14	2.01 (0.98–4.10)

NOTE: U-TCA = urinary metabolite of trichloroethylene.
[a]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.

HEPATOBILIARY CANCERS

Description of Case–Control Studies

Two population-based (Hardell et al., 1984; Heinemann et al., 2000) and two hospital-based (Hernberg et al., 1988; Stemhagen et al., 1983) case–control studies examined risk of liver cancer associated with occupational exposure to solvents (Table 6.12). Self-administered questionnaires or interviews were used to obtain occupational history information in each study. The study by Stemhagen and colleagues (1983) used job titles as surrogates of exposure. In two of the other studies, exposures were inferred by industrial hygienists (Heinemann et al., 2000; Hernberg et al., 1988). In the two hospital-based studies, there were no adjustments for potentially confounding variables.

Epidemiologic Studies of Exposure to Organic Solvents and Hepatobiliary Cancers

Anttila and colleagues (1995) found an increased risk (SIR = 2.27, 95% CI = 0.74–5.29) of liver cancer in the cohort of workers biologically monitored for a metabolite of trichloroethylene. Likewise, Hansen and colleagues (2001) reported an increased risk of cancer of the liver and biliary passages in men in a Danish cohort of biologically monitored workers (SIR = 2.6, 95% CI = 0.8–6.0).

In a large cohort study of aircraft-manufacturing workers in California, Boice and colleagues (1999) found no association between liver cancer and exposure to trichloroethylene (SMR = 0.54, 95% CI = 0.15–1.38). Another cohort of aircraft manufacturers (Morgan et al., 1998) showed no increased mortality in trichloroethylene-exposed workers, and there was no evidence of a trend in mortality with cumulative exposure.

In the cohort of workers at Hill Air Force Base in Utah, Blair and colleagues (1998) did not find excess risk of liver cancer mortality or incidence, nor was there any apparent increase with increasing cumulative exposure to trichloroethylene.

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TABLE 6.12 Description of Case–Control Studies of Liver Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Stemhagen et al., 1983	Cases identified through diagnosis in New Jersey hospitals in 1975–1980 or from death certificates in 1975–1979, all with histologic confirmation; controls selected from hospital records and death certificates and matched for age, race, sex, county of residence Response rates: 89.5% of cases, 77% of controls	265	530	Laundering, cleaning, other garment service work	In-person interview (direct or proxy) to assess occupational history (job titles)	OR	None
Hardell et al., 1984	Deceased male cases, age 25–80 years at diagnosis, reported to the Swedish Cancer Registry and diagnosed in 1974–1981, with histologic confirmation; controls selected from the National Population Register, matched on sex, age, year of death, municipality	98	200	Organic solvents	Mailed questionnaires to next of kin, assessing work history (job titles) and occupational or leisure-time exposure to specific chemicals (self-reports)	Mantel-Haenszel rate ratio, Miettinen 95% CI	Age
Hernberg et al., 1988	Deceased cases, reported to the Finnish Cancer Register in 1976–1978 and 1981; controls selected from deceased stomach-cancer cases and coronary-infarction patients reported in 1977 Response rates: 71.7% of cases, 72.8% of stomach-cancer controls, 69.0% of infarction controls	344	476 stomach 385 coronary infarction	Solvents	Questionnaire mailed to next of kin to elicit list of occupations and employers; hygienist assigned exposure classification based on occupation	Likelihood-based ORs	None
Heinemann et al., 2000	Female cases, under 65 years old, identified at 64 clinics in six European countries in 1990–1994 (prevalent cases) and 1994–1996 (incident cases); hospital controls selected from respective clinics and matched on age; population controls selected from citizen registers	317	1,779	Dry-cleaning work Solvents	In-person interview (direct or proxy) with questionnaire assessing occupational history (industry titles) and specific agent exposures (self-reports)	Logistic regression	Age, center, smoking, alcohol, oral contraceptive use, hepatitis infection

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Ritz (1999) found associations between exposure to trichloroethylene and liver cancer among male workers in the uranium-processing industry (SMR = 1.66, 95% CI = 0.71–3.26). The association is based on a small number of cases and may be confounded by other potential exposures involved in uranium processing. Axelson and colleagues (1994) also found an increased incidence in male Swedish workers exposed to trichloroethylene (SIR = 1.41, 95% CI = 0.38–3.60). A cohort study of transformer-assembly workers (Greenland et al., 1994) showed no positive associations between occupational exposure to trichloroethylene and cancers of the liver, gallbladder, and biliary tract combined (OR = 0.54, 95% CI = 0.11–2.63).

In the cohort of aircraft-manufacturing workers (Boice et al., 1999), an association between exposure to tetrachloroethylene and liver cancer was observed (SMR = 2.05, 95% CI = 0.83–4.23) but no increase was observed with increasing duration of exposure. Bond and colleagues (1990) found an association between mortality and liver cancer in a cohort of chemical workers (OR = 1.8, 95% CI = 0.8–4.3).

A cohort study of US dry cleaners showed no association to liver cancer (SMR = 0.7, 95% CI = 0.2–1.7) (Blair et al., 1990). Ruder and colleagues (2001) detected only one case of liver cancer among the subcohort of workers exposed to tetrachloroethylene and other solvents (SMR = 0.16, 95% CI = 0.00–1.32).

In a case–control study of women in the Multicentre International Liver Tumour Study, three women with hepatocellular cancer reported working as dry cleaners (OR = 0.65; 95% CI = 0.12–3.44) (Heinemann et al., 2000). Another study of occupational risk factors for liver cancer found an association among men employed in laundering, cleaning, and other garment services (RR = 2.5, 95% CI = 1.02–6.14) (Stemhagen et al., 1983). Further investigation by the authors showed that the cases were concentrated among people who processed clothes and potentially had exposure to other chemicals.

Friedlander and colleagues (1978) established a cohort of workers in one department at Kodak where methylene chloride was the primary solvent exposure for more than 30 years. In the most recent followup (Hearne and Pifer, 1999), one death from liver cancer was observed (SMR = 0.42, 95% CI = 0.01–2.36).

A cohort study of workers producing cellulose triacetate fibers at a Hoechst Celanese plant in South Carolina showed an excess risk of biliary and liver cancers (SMR = 2.98, 95% CI = 0.81–7.63) (Lanes et al., 1993). In another Hoechst Celanese facility manufacturing cellulose triacetate, Gibbs and colleagues (1996) found one death from liver cancer (SMR = 0.81, 95% CI = 0.02–4.49).

No cases of liver cancer were found in a cohort of male workers producing cellulose triacetate film base at a plant in the UK (Tomenson et al., 1997). A nested case–control study of liver and biliary tract cancer cases identified among male hourly employees of the Dow Chemical Company did not show an excess risk in workers exposed to methylene chloride (RR = 0.8, 95% CI = 0.2–3.6) (Bond et al., 1990).

Yin and colleagues (1996a,b) followed a cohort of factory workers with known exposure to benzene. Increased relative risks of cancers of the liver and gallbladder combined were reported for men (RR = 1.3, 95% CI = 0.9–1.9) but not for women (RR = 0.4, 95% CI = 0.2–1.3). This cohort was further examined by Hayes and colleagues (1996), who evaluated the relative risks according to cumulative exposure to benzene. There was some suggestion that the relative risks for liver and gallbladder cancer increased with increasing cumulative exposure, although chance could not be ruled out confidently (*p* value for linear trend = 0.16).

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A nested case–control study by Greenland and colleagues (1994) of transformer-assembly workers exposed to benzene showed a positive association between occupational exposure to benzene and cancers of the liver, gallbladder, and biliary tract combined (OR = 2.76, 95% CI = 0.68–11.2).

A cohort of toluene-exposed German rotogravure workers studied by Wiebelt and Becker (1999) experienced a higher risk of liver cancer mortality than the population of West Germany (SMR = 1.98, 95% CI = 0.34–7.16). Dosemeci and colleagues (1991) conducted a study of US industrial workers that showed no increase in liver cancer mortality among those occupationally exposed to phenol (SMR = 1.0, 95% CI = 0.4–1.9). The association with phenol did not increase markedly from low to medium to high exposure.

Three population-based case–control studies (Hardell et al., 1984; Heinemann et al., 2000; Hernberg et al., 1988) examined the association of liver cancer in relation to the broad category of solvents or mixed solvents. Heinemann and colleagues (2000) found no associations (OR = 1.05, 95% CI = 0.52–2.09). Hernberg and colleagues (1988) did not find increased risks among males (OR = 0.6, 90% CI 0.3–1.3), but increased risks were found among women (OR = 3.4, 90% CI 1.3–8.6). Hardell and colleagues (1984) also found an association (OR = 1.8, 95% CI = 0.99–3.4).

In the cohort studies, no associations were found in aircraft-manufacturing workers (SMR = 0.92) (Boice et al., 1999), but the three cohort studies of painters all showed excess risks of liver cancer: Steenland and Palu (1999) found an SMR of 1.25 (95% CI = 1.03–1.50), Matanoski and colleagues (1986) an SMR of 1.47 (95% CI = 0.98–2.13), and Morgan (1981) an SMR of 1.93.

Summary and Conclusion

Although most studies examined the risk for liver cancer broadly, others combined liver cancer with gallbladder and biliary tract cancers. For exposure to trichloroethylene, tetrachloroethylene and dry-cleaning solvents, toluene, and phenol, most studies did not find an increased risk. Although one study on methylene chloride found a positive association, the small number of cases of liver cancer and the lack of corroborating studies were limitations of the literature. The studies on exposure to benzene were also limited with only three studies of benzene-exposed workers (two of which were on the same cohort), and only weak evidence of excess risks. For exposure to unspecified mixtures of organic solvents, although some of the estimates of risk were positive, others were not, and the role of confounding by other exposures or risk factors was a limitation. Table 6.13 identifies the key studies and the relevant data points reviewed by the committee in drawing its conclusion. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and hepatobiliary cancers.

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TABLE 6.13 Selected Epidemiologic Studies—Hepatobiliary Cancers and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males	5	2.6 (0.8–6.0)
	Females	0	—
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Males:		
	No exposure	1	0.8 (0.1–12.0)
	<5 unit-years	2	1.2 (0.1–13.8)
	5–25 unit-years	1	1.0 (0.1–16.0)
	>25 unit-years	3	2.6 (0.3–25.0)
Anttila et al., 1995	Biologically monitored workers in Finland		
	Entire period since first measurement:	5	2.27 (0.74–5.29)
	0–9 years	0	— (0.0–6.59)
	10–19 years	2	1.74 (0.21–6.29)
	≥20 years	3	6.07 (1.25–17.7)
	Mean personal U-TCA level		
	<100 μmol/L	2	1.64 (0.20–5.92)
	100+ μmol/L	2	2.74 (0.33–9.88)
Axelson et al., 1994	Biologically monitored Swedish workers	4	1.41 (0.38–3.60)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	All exposed factory workers	4	0.54 (0.15–1.38)
	Duration of potential exposure (routine or intermittent)		
	<1 year	4	0.53 (0.18–1.60)
	1–4 years	3	0.52 (0.15–1.79)
	≥ 5 years	6	0.94 (0.36–2.46)
Ritz, 1999	White male US uranium-processing plant workers		
	Trichloroethylene, cutting fluids, or kerosene	8	1.66 (0.71–3.26)
	Trichloroethylene—light exposure		
	>2 years, no latency	3	0.93 (0.19–4.53)
	>2 years, 15-year latency	3	1.16 (0.24–5.60)
	>5 years, no latency	3	1.90 (0.35–10.3)
	>5 years, 15-year latency	3	2.86 (0.48–17.3)
	Trichloroethylene—moderate exposure		
	>2 years, no latency	1	4.97 (0.48–51.1)
	>2 years, 15-year latency	1	5.53 (0.54–56.9)
	>5 years, no latency	1	8.82 (0.79–98.6)
	>5 years, 15-year latency	1	12.1 (1.03–144)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Males		
	No exposure	3	0.5 (0.1–2.4)
	<5 unit-years	6	1.1 (0.3–4.1)
	5–25 unit-years	3	0.9 (0.2–4.3)
	>25 unit-years	3	0.7 (0.2–3.2)
	Females:		
	No exposure	3	4.2 (0.7–25.0)
	<5 unit-years	1	1.6 (0.2–18.2)
	5–25 unit-years	0	—
	>25 unit-years	2	2.3 (0.3–16.7)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Morgan et al., 1998	Aerospace workers in Arizona		
	Trichloroethylene-exposed subcohort:	6	0.98 (0.36–2.13)
	Low cumulative exposure	3	1.32 (0.27–3.85)
	High cumulative exposure	3	0.78 (0.16–2.28)
	Peak and cumulative exposure:[a]		
	Peak: medium and high vs low and no exposure	3	0.98 (0.29–3.35)
	Cumulative (low)	3	2.12 (0.59–7.66)
	Cumulative (high)	3	1.19 (0.34–4.16)
Greenland et al., 1994	White male transformer-assembly workers, ever exposed	NA	0.54 (0.11–2.63)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	US dry-cleaning workers in four labor unions	1	0.16 (0.00–1.32)
Boice et al., 1999	Aircraft- manufacturing workers		
	All exposed factory workers	7	2.05 (0.83–4.23)
	Duration of potential exposure (routine or intermittent)		
	<1 year	3	1.38 (0.40–4.69)
	1–4 years	4	0.39 (0.39–3.47)
	≥5 years	5	1.29 (0.46–3.65)
Blair et al., 1990	Dry-cleaning union members in Missouri	5	0.7 (0.2–1.7)
Bond et al., 1990	Male chemical-company workers in Michigan, ever exposed	6	1.8 (0.8–4.3)
Case–Control Studies			
Heinemann et al., 2000	Females in the Multicentre International Liver Tumour Study		
	Dry-cleaning, ever employed	3	0.65 (0.12–3.44)
Stemhagen et al., 1983	Laundering, cleaning, other garment-services workers in New Jersey, employed >6 months	10	2.50 (1.02–6.14)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne and Pifer, 1999	Male cellulose triacetate photographic-film base workers in Kodak Park, employed >1 year	1	0.42 (0.01–2.36)
Tomenson et al., 1997	Male cellulose triacetate-fiber film base workers in the UK		
	Never exposed	0	—
	All exposed	0	—
Gibbs et al., 1996	Male cellulose triacetate-fiber production workers in Maryland		
	No exposure	0	—
	Low exposure	1	0.75 (0.029–4.20)
	High exposure	1	0.81 (0.020–4.49)
Lanes et al., 1993	Cellulose triacetate-fiber production workers in South Carolina, employed >3 months	4	2.98 (0.81–7.63)
Bond et al., 1990	Male chemical-company workers in Michigan, ever exposed	2	0.8 (0.2–3.6)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Studies—Mortality			
Yin et al., 1996a	Chinese factory workers, ever exposed		
	Total cohort	109	1.2 (0.8–1.6)
	Men	101	1.3 (0.9–1.9)
	Women	8	0.4 (0.2–1.3)
Hayes et al., 1996	Chinese factory workers		
	<10 ppm-years	12	1.1
	10–39 ppm-years	12	0.8
	40–99 ppm-years	9	0.6
	100–400 ppm-years	44	1.6
	400+ ppm-years	28	1.2
			p-trend = 0.16
Greenland et al., 1994	White male transformer-assembly workers, ever exposed	NA	2.76 (0.68–11.2)
Other Specific Organic Solvents			
Cohort Studies—Mortality			
Wiebelt and Becker, 1999	Male German rotogravure printing-plant workers, employed >1 year—toluene	3	1.98 (0.34–7.16)
Dosemeci et al., 1991	US white male industrial workers—phenol		
	Any exposure	8	1.0 (0.4–1.9)
	Level of cumulative exposure:		
	None	4	1.2
	Low exposure	1	0.3
	Medium exposure	6	1.6
	High exposure	1	1.4
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers		
	All exposed factory workers	17	0.92 (0.54–1.47)
	Duration of potential exposure (routine or intermittent)		
	<1 year	10	1.35 (0.63–2.87)
	1–4 years	14	0.75 (0.38–1.47)
	≥ 5 years	31	0.97 (0.54–1.72)
Steenland and Palu, 1999	Members of US painters' unions		
	Total cohort	119	1.25 (1.03–1.50)
	20 years since first union membership	90	1.17 (0.95–1.44)
Greenland et al., 1994	White male transformer-assembly workers, ever exposed to solvents	NA	0.69 (0.18–2.60)
Matanoski et al., 1986	US painters and allied tradesmen	28	1.47 (0.98–2.13)
Morgan et al., 1981	Male US paint or varnish manufacturing workers, employed >1 year	6	1.93
Case–Control Studies			
Heinemann et al., 2000	Women in Multicentre International Liver Tumor Study, ever exposed to solvents	18	1.05 (0.52–2.09)
Hernberg et al., 1988	Finnish cases and deceased controls		
	Solvent exposure, 10-year latency		
	Males	7	0.6 (0.3–1.3)[b]
	Females	7	3.4 (1.3–8.6)[b]

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Hardell et al., 1984	Male residents of Sweden		
	High-grade exposure to organic solvents		
	Primary liver cancer	22	1.8 (0.99–3.4)
	Hepatocellular carcinoma	20	2.1 (1.1–4.0)

NOTE: NA = not available; U-TCA = urinary metabolite of trichloroethylene.
[a]Internal cohort analyses for peak and cumulative exposure to trichloroethylene classifications used Cox proportional-hazards models.
[b]90% CI.

LUNG CANCER

Description of Case–Control Studies

Three population-based case–control studies (Table 6.14) reported the risk of lung cancer associated with job title and self-reported exposure to specific chemicals (Brownson et al., 1993; Pohlabeln et al., 2000) or to tetrachloroethylene in drinking water (Paulu et al., 1999). Smoking is a known risk factor for lung cancer and was accounted for in each of the studies (see Chapter 2 and Appendix E for more information on smoking).

Epidemiologic Studies of Exposure to Organic Solvents and Lung Cancer

No association was found between incidence of lung cancer and concentrations of the biologic marker of exposure to trichloroethylene (SIR = 0.92, 95% CI = 0.59–1.35) (Anttila et al., 1995). A cohort of aircraft-manufacturing workers with potential exposure to trichloroethylene was followed for nearly 30 years, but no association between lung cancer and trichloroethylene was reported (SMR = 0.76, 95% CI = 0.60–0.95) (Boice et al., 1999). The authors noted that most workers were exposed to a variety of substances routinely or intermittently. A mortality study of civilian aircraft-maintenance workers at Hill Air Force Base in Utah that included an extensive assessment of exposure to trichloroethylene did not show an increase in lung cancer mortality or incidence in men (over 25 unit-years: SMR = 1.1, 95% CI = 0.7–1.8) or women (over 25 unit-years: SMR = 0.4, 95% CI = 0.1–1.8) (Blair et al., 1998). The cohort study of aircraft manufacturers in Arizona (Morgan et al., 1998) did not show increased mortality from lung cancer in the trichloroethylene-exposed subcohort (SMR = 1.10, 95% CI = 0.89–1.34).

In addition to those studies, no associations were found for rubber-industry workers exposed to trichloroethylene (OR = 0.64) (Wilcosky et al., 1984) or to transformer-assembly workers (OR = 1.01, 95% CI = 0.69–1.47) (Greenland et al., 1994).

A cohort study of dry-cleaning workers exposed to tetrachloroethylene and other solvents showed increased mortality from lung cancer (SMR = 1.46, 95% CI = 1.07–1.95) (Ruder et al., 2001). In the subcohort of workers exposed only to tetrachloroethylene, the relative risks were not as great (SMR = 1.17, 95% CI = 0.71–1.83). Blair and colleagues (1990) reported a comparable relative risk of lung cancer in another cohort of dry cleaners (SMR = 1.3, 95% CI = 0.9–1.7).

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TABLE 6.14 Description of Case–Control Studies of Lung Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Brownson et al., 1993	White, female cases, age 30–84 years, identified through the Missouri Cancer Registry as diagnosed in 1986–1991, with 77% histologic confirmation; controls younger than 65 years selected from state driver's license files; controls older than 65 years were selected from the records of HCFA Response rates: 66% of cases, 67% of controls	429	1,021	Dry-cleaning work Printing-industry work	Trained interviewers conducted telephone and in-person interviews (direct or proxy) to assess specific occupational (job titles) and exposure history (self-reported)	Multiple logistic regression	Age, history of lung disease, active smoking
Paulu et al., 1999	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from the records of HCFA and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 79% of cases, 76% of HCFA controls, 74% of RDD controls, 79% of next of kin of deceased controls	243	1,206	Tetrachloro-ethylene	Exposure dose estimated in areas of contaminated drinking water, accounting for location and years of residence, water flow, pipe characteristics	Multiple logistic regression	Age at diagnosis, vital status, sex, occupational exposure to solvents; specific cancer risk factors controlled in respective analyses, such as smoking
Pohlabeln et al., 2000	Nonsmoking cases identified in 12 study centers from seven European countries between 1988–1994 (96.5% were histologically confirmed); community-based controls were selected in six centers, hospital-based controls in five centers, and both community and hospital-based controls in one center Response rates: across centers the rate varied between 55% and 95%; in three centers, the response rate among control subjects was lower than 50%	650	1,542	Laundry and dry cleaners	Interviewers used a common questionnaire to record lifelong occupational histories which were coded by job titles	Unconditional logistic regression	Sex, occupation, age, center, occasional smoking (ever smoked occasionally, but fewer than 400 cigarettes), residence, diet, and environmental tobacco smoke

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing.

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An increased risk of lung cancer was found in workers exposed to tetrachloroethylene (SIR = 1.92, 95% CI = 0.62–4.48) (Anttila et al., 1995). Among the cohort of aircraft manufacturers, no association was found between exposure to tetrachloroethylene and lung cancer (SMR = 1.08, 95% CI = 0.79–1.44) (Boice et al., 1999). The authors indicated that concentrations of tetrachloroethylene in the air samples were relatively low and that exposures were well below permissible concentrations. Wilcosky and colleagues (1984), in a study of rubber-industry workers, reported no increased risk of lung cancer with exposure to tetrachloroethylene.

The risk of developing lung cancer in relation to exposure to tetrachloroethylene was evaluated in the two case–control studies, and these were adjusted for smoking. A risk associated with self-reported exposure to tetrachloroethylene was found among lifetime nonsmokers (OR = 2.1, 95% CI = 1.2–3.7) (Brownson et al., 1993). A case–control study of residents of upper Cape Cod (Paulu et al., 1999) showed excess risks of lung cancer with increasing level of estimated exposure to tetrachloroethylene in drinking water. A third case–control study of female, nonsmoking laundry and dry cleaners also found an increased risk of lung cancer (OR = 1.83, 95% CI = 0.98–3.40) (Pohlabeln et al., 2000).

Several cohort studies of workers exposed to methylene chloride provided little support for an association between exposure and lung cancer (Gibbs et al., 1996; Hearne and Pifer, 1999; Hearne and Friedlander, 1981; Hearne et al., 1987, 1990; Lanes et al., 1990, 1993; Tomenson et al., 1997). Those large cohort studies followed methylene chloride-exposed workers for many years, some with repeated followup, and examined the association between exposure and cancer mortality, but they reveal no excess of lung cancer associated with exposure.

Yin and colleagues (1996a,b) reported increased relative risks of cancers of the trachea, bronchi, and lung combined in benzene-exposed males (RR = 1.5, 95% CI = 1.0–2.2) and in the entire cohort of exposed men and women (RR = 1.4, 95% CI = 1.0–2.0); no association was found in benzene-exposed women (RR = 1.0, 95% CI = 0.4–2.9). Hayes and colleagues (1996) assessed the cumulative exposure to benzene in the overall cohort and found that the relative risks of tracheal, bronchial, and lung cancers combined increased with increasing exposure (p trend = 0.01).

Two nested case–control studies, one of transformer-assembly workers (Greenland et al., 1994) and another of rubber-industry workers (Wilcosky et al., 1984), did not show any associations between occupational exposure to benzene and lung cancer. No data were presented on increasing levels of exposure.

Three studies provided evidence on the association between toluene and lung cancer. A cohort of toluene-exposed German rotogravure workers showed increased lung cancer mortality when compared with the mortality in West Germany (SMR = 1.23, 95% CI = 0.81–1.92) (Wiebelt and Becker, 1999). Job-specific subcohorts with different levels of exposure to toluene demonstrated a range of lung cancer risk, from no risk in printing-cylinder preparation occupations to an SMR of 1.77 (95% CI = 0.77–4.39) in finishing workers who had the lowest level of exposure over the entire observation period.

A Swedish cohort of rotogravure printers showed similar increases in respiratory tract cancer mortality from exposure to toluene (SMR = 1.76, 95% CI = 1.03–2.91) (Svensson et al., 1990); however, no gradient was found with duration of exposure.

Factory workers who were considered to have high exposure in a plant manufacturing chlorinated toluenes (benzyl chloride, benzal chloride, benzotrichloride, and benzoyl chloride) experienced increased lung cancer mortality (SMR = 3.31, 95% CI = 1.59–6.09) (Sorahan and

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Cathcart, 1989), and there was evidence that risk increased with increasing exposure. In a nested case–control study of 26 cases of lung cancer from the cohort of chlorinated toluene production workers, RR of lung cancer associated with benzotrichloride and "other chlorinated toluenes" was 1.36 (95% CI = 0.43–4.24) and 1.12 (95% CI = 0.30–4.22), respectively, per 10 years of exposed employment. In a study of rubber workers, Wilcosky and colleagues (1984) did not find an association (OR = 0.55).

There were three studies of the association between exposure to phenol and lung cancer. A cohort study with many exposed cases showed no association (Dosemeci et al., 1991), and no association was reported for workers in the rubber industry (Wilcosky et al., 1984). Kauppinen and colleagues (1993) reported a four-fold excess risk (SMR = 4.04, 95% CI = 1.83–8.89) after adjusting for smoking among those exposed for at least 1 month.

Several other solvents used in the Gulf War—including naphtha, ethanol, xylenes, isopropanol, ethyl acetate, and acetone (Wilcosky et al., 1984)—were investigated in relation to lung cancer, and no associations with these solvents were found. Anttila and colleagues (1995) found an increase in lung and bronchial cancer risk with exposure to 1,1,1-trichloroethane (SIR = 1.31, 95% CI = 0.16–4.71).

Several studies, including some described previously, examined the association of lung cancer with unspecified mixtures of solvents. Most studies did not identify "solvents" or "organic solvents" as the exposure being evaluated but instead defined exposure by various occupational titles or groups, such as painters (Engholm and Englund, 1982; Englund 1980; Matanoski et al., 1986; Morgan et al., 1981; Steenland and Palu, 1999; Stockwell and Matanoski, 1985), printers (Malker and Gemne, 1987), workers in transformer assembly (Greenland et al., 1994), ethanol and isopropanol production (Teta et al., 1992), isopropanol and methyl ethyl ketone production (Alderson and Rattan, 1980), shoe manufacturing (Walker et al., 1993), chemical manufacturing (Waxweiler et al., 1981), aircraft manufacturing (Boice et al., 1999), or metal-component manufacturing (Acquavella et al., 1993). As shown in Table 6.15, many of the studies showed positive associations between occupational exposure and lung cancer.

Generally, workers in the studies were exposed to solvents and other chemical agents not reviewed by this committee. More important, although smoking is associated with lung cancer, no adjustments for it were made in most cohort studies. (That is not unusual; obtaining smoking histories, especially in mortality studies, is difficult.) Furthermore, one study that specifically examined lung cancer risk among nonsmokers in the printing industry found no association with occupational exposure (Brownson et al., 1993). Unlike farm workers, who have some of the lowest smoking rates in the United States, painters, truck drivers, construction workers, carpenters, and auto mechanics have some of the highest rates. For example, in a National Center for Health Statistics survey of men 20–64 years old in 1978–1980, 55.1% of painters surveyed reported that they smoked (US Surgeon General, 1985).

To understand the impact of smoking on risk of lung cancer, the committee examined the risk estimates for bladder cancer and cardiovascular disease—diseases for which smoking is also a known risk factor. Almost all the studies reported rates of bladder cancer and cardiovascular disease similar to those of lung cancer. Almost all the studies also stated that asbestos was present in the workplace and probably contributed to the slightly increased observed risks of lung cancer. As a result, the committee determined that exposure to solvents alone was an unlikely explanation for the increased risks of lung cancer and that confounding by smoking was possibly biasing the results.

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Summary and Conclusion

Although there are different types of respiratory cancers, most studies assessed exposure in relation to lung cancer. Exposures were typically defined by occupations in which the solvents were known to be present; and confounding factors, especially smoking, were not consistently controlled for in the analyses. In reviewing the literature, the committee found that there was no evidence from any of the studies of a positive association between exposure to trichloroethylene, methylene chloride, benzene, phenol, and other specific solvents and risk of lung cancer.

For exposure to tetrachloroethylene and dry-cleaning solvents, some committee members believed that the overall evidence was limited by the possibility of confounding, and that most findings were based on small numbers of cases exposed by different routes. The cohort studies did not control for other occupational exposures or smoking, an important potential confounder for lung cancer. However, other committee members believed that the consistently positive findings and evidence of a dose-response relationship in the case–control study by Paulu and colleagues were supportive of a conclusion of limited/suggestive evidence. Both case–control studies adjusted for smoking and still found relatively high relative risks of lung cancer. As a result, the committee decided not to state a formal consensus conclusion. Additional studies that control for smoking and address other concerns related to misclassification of exposure are needed before a more definitive conclusion as to exposure to tetrachloroethylene and dry-cleaning solvents and the risk of lung cancer can be reached.

Although several cohort studies reported increased risk of lung cancer associated with exposure to toluene, estimates were weak. Workers were probably exposed to other compounds that were not controlled for in the analyses. In addition, information on smoking was not available. A unique relationship between solvent exposure and lung cancer was not found, and the committee concluded that the evidence was inadequate/insufficient to support an association between exposure to unspecified mixtures of organic solvents and lung cancer.

Several studies on specific organic solvents and solvent mixtures found positive associations between exposure and the risk of lung cancer. However, most studies on specific solvents were too small and inconsistent in their findings to support conclusions. Some studies showed positive associations, but they were limited by lack of information on smoking habits among cohort members.

With respect to exposure to solvent mixtures, many studies reported positive findings; most, however, were based on occupational titles or industries and lacked specific analyses of "solvents" or "organic solvents." Although their results suggested a possible relationship, the lack of smoking data, the lack of exposure specificity, and the potential for confounding by other occupational exposures (such as to asbestos) limited their utility. Future research with sufficient power would help to clarify whether an association between exposure to solvent mixtures or the interactions of various solvents and lung cancer exists, as is indicated in some of the studies reviewed by the committee. Table 6.15 identifies the key studies and the relevant data points evaluated by the committee in drawing its conclusion. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than tetrachloroethylene and dry-cleaning solvents, and lung cancer.

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TABLE 6.15 Selected Epidemiologic Studies—Lung Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Males		
	No exposure	22	1.0 (0.5–1.9)
	<5 unit-years	24	1.0 (0.6–2.0)
	5–25 unit-years	11	0.8 (0.4–1.6)
	>25 unit-years	15	0.8 (0.4–1.7)
	Females		
	No exposure	0	—
	<5 unit-years	1	0.6 (0.1–5.3)
	5–25 unit-years	0	—
	>25 unit-years	0	—
Anttila et al., 1995	Biologically monitored workers in Finland		
	Entire period since first measurement	25	0.92 (0.59–1.35)
	0–9 years	11	1.19 (0.59–2.13)
	10–19 years	9	0.67 (0.30–1.26)
	≥20 years	5	1.11 (0.36–2.58)
	Mean personal U-TCA level		
	<100 μmol/L	16	1.02 (0.58–1.66)
	100+ μmol/L	7	0.83 (0.33–1.71)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	All exposed factory workers	78	0.76 (0.60–0.95)
	Duration of potential exposure (routine or intermittent)		
	<1 year	66	0.85 (0.65–1.13)
	1–4 years	63	0.98 (0.74–1.30)
	≥5 years	44	0.64 (0.46–0.89)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Males		
	No exposure	51	1.0 (0.7–1.6)
	<5 unit-years	43	1.0 (0.6–1.6)
	5–25 unit-years	23	0.9 (0.5–1.6)
	>25 unit-years	38	1.1 (0.7–1.8)
	Females		
	No exposure	2	0.4 (0.1–1.6)
	<5 unit-years	2	0.6 (0.1–2.4)
	5–25 unit-years	11	0.6 (0.1–4.7)
	>25 unit-years	2	0.4 (0.1–1.8)
Morgan et al., 1998	Aerospace workers in Arizona		
	Entire trichloroethylene-exposed cohort	97	1.10 (0.89–1.34)
	Cumulative		
	Low	45	1.49 (1.09–1.99)
	High	52	0.90 (0.67–1.20)
	Peak: medium and high vs low and no exposure	64	1.07 (0.82–1.40)
Greenland et al., 1994	White male transformer-assembly workers, ever exposed	NA	1.01 (0.69–1.47)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Wilcosky et al., 1984	Rubber-industry workers in Ohio		
	Cumulative exposure of more than 1 year		
	White males	11	0.64
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	US dry-cleaning workers in four labor unions		
	Males, nonwhite	25	1.52 (1.05–2.39)
	Females, nonwhite	16	1.88 (1.07–3.05)
	Exposed to tetrachloroethylene only	19	1.17 (0.71–1.83)
	Exposed to tetrachloroethylene and other dry-cleaning solvents	46	1.46 (1.07–1.95)
Boice et al., 1999	Aircraft manufacturing workers in California		
	All exposed factory workers	46	1.08 (0.79–1.44)
	Duration of potential exposure (routine or intermittent)		
	<1 year	33	1.15 (0.80–1.66)
	1–4 years	51	1.09 (0.80–1.48)
	≥ 5 years	36	0.71 (0.49–1.02)
Anttila et al., 1995	Biologically monitored workers in Finland	5	1.92 (0.62–4.48)
Blair et al., 1990	Dry-cleaning union members in Missouri	47	1.3 (0.9–1.7)
Wilcosky et al., 1984	Rubber-industry workers in Ohio		
	Cumulative exposure of more than 1 year		
	White males	2	0.26
Case–Control Studies			
Pohlabeln et al., 2000	Occupational exposure among nonsmoking females in Europe		
	Laundry and dry cleaners for at least 6 months	19	1.83 (0.98–3.40)
Paulu et al., 1999	Residents in upper Cape Cod		
	>75th percentile tetrachloroethylene–water exposure		
	0-year latent period	11	1.8 (0.8–3.9)
	5-year latent period	6	1.7 (0.6–4.5)
	7-year latent period	5	1.6 (0.5–4.4)
	9-year latent period	4	1.8 (0.5–6.0)
	>90th percentile tetrachloroethylene–water exposure		
	0-year latent period	5	3.7 (1.0–11.7)
	5-year latent period	3	3.3 (0.6–13.4)
	7-year latent period	3	6.2 (1.1–31.6)
	9-year latent period	3	19.3 (2.5–141.7)
Brownson et al., 1993	Occupational exposure among females in Missouri—Dry-cleaning		
	Lifetime nonsmokers	23	2.1 (1.2–3.7)
	Exposure range		
	Low: ≤ 1.125 years	NA	0.6 (0.2–1.7)
	High: ≥ 1.125 years	NA	2.9 (1.5–5.4)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne et al., 1999	Male cellulose triacetate photographic-film base workers in Kodak Park, employed >1 year		
	Methylene chloride cohort	27	0.75 (0.49–1.09)
	Roll-coating cohort		
	New York state external control	28	0.82 (0.55–1.19)
	Kodak Rochester external control	28	0.89 (0.59–1.29)
Tomensen et al., 1997	Male cellulose triacetate-fiber production workers in the UK, ever employed		
	Never exposed	1	0.16 (0–0.88)
	All exposed	19	0.48 (0.29–0.75)
	Cumulative exposure (nonsmokers)		
	<400 ppm-years	6	0.32
	400–799 ppm-years	2	0.51
	≥800 ppm-years	1	0.37
	Unassigned exposure	10	0.68
Gibbs et al., 1996	Cellulose triacetate-fiber production workers in Maryland		
	Males		
	No exposure	6	0.59 (0.22–1.29)
	Low exposure	20	0.78 (0.48–1.20)
	High exposure	15	0.55 (0.31–0.91)
	Females		
	No exposure	0	NA (0.0–4.92)
	Low exposure	9	1.09 (0.50–2.07)
	High exposure	2	2.29 (0.28–8.29)
Lanes et al., 1993	Cellulose triacetate-fiber production workers in South Carolina (cohort), employed >3 months	13	0.80 (0.43–1.37)
Benzene			
Cohort Studies—Mortality			
Yin et al., 1996a	Chinese factory workers, ever exposed		
	Total cohort	125	1.4 (1.0–2.0)
	Males	109	1.5 (1.0–2.2)
	Females	16	1.0 (0.4–2.9)
Hayes et al., 1996	Chinese factory workers		
	Cumulative exposure		
	No exposure	41	1.0
	<10 ppm-years	10	1.2
	10–39 ppm-years	13	1.0
	40–99 ppm-years	19	1.4
	100–400 ppm-years	38	1.4
	400+ ppm-years	41	1.7
			p-trend = 0.01
Greenland et al., 1994	White male transformer-assembly workers, ever exposed	NA	0.58 (0.31–1.07)
Wilcosky et al., 1984	Rubber-industry workers in Ohio		
	Cumulative exposure of more than 1 year		
	White males	23	0.69

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Toluene			
Cohort Studies—Mortality			
Wiebelt and Becker, 1999	Male German rotogravure printing-plant workers, employed >1 year		
	Total cohort	44	1.23 (0.81–1.92)
	Printing-cylinder preparation workers	7	0.83 (0.20–2.77)
	Printing/proof printing workers	25	1.30 (0.72–2.49)
	Finishing workers	13	1.77 (0.77–4.39)
Svensson et al., 1990	Male rotogravure printing-plant workers in Sweden		
	Total cohort	16	1.76 (1.03–2.91)
	≥5 year exposure, >10 year latency	9	1.26 (0.57–2.38)
Sorahan and Cathcart, 1989	Male chemical-factory workers		
	Low exposure to chlorinated toluenes	16	1.39 (0.80–2.27)[a]
	High exposure to chlorinated toluenes	10	3.31 (1.59–6.09)[a]
	Benzotrichloride	NA	1.36 (0.43–4.24)
	Other chlorinated toluenes	NA	1.12 (0.30–4.22)
Wilcosky et al., 1984	White, male rubber-industry workers in Ohio		
	Cumulative exposure for more than 1 year	3	0.55
Phenol			
Cohort Studies—Mortality			
Kauppinen et al., 1993	Finnish woodworkers		
	Any exposure (>1 month)	5	4.04 (1.83–8.89)
	Duration >5 years	6	3.08 (0.70–13.6)
Dosemeci et al., 1991	US white male industrial workers		
	Any exposure	146	1.1 (0.9–1.3)
	Level of cumulative exposure		
	None	70	1.2
	Low exposure	68	1.2
	Medium exposure	60	1.1
	High exposure	18	1.4
Wilcosky et al., 1984	White male rubber-industry workers in Ohio		
	Cumulative exposure for more than 1 year		
	White males	13	0.95
	Black males	2	0.91
Other Organic Solvents			
Cohort Studies—Mortality			
Anttila et al., 1995	Biologically monitored workers in Finland		
	1,1,1-trichloroethane ever measured in urine	2	1.31 (0.16–4.71)
Wilcosky et al., 1984	Rubber-industry workers in Ohio		
	Cumulative exposure for more than 1 year		
	Specialty naphthas (white males)	43	0.70
	Specialty naphthas (black males)	2	0.39
	Ethanol (white males)	21	1.0
	Xylenes (white males)	10	0.61
	Ethyl acetate (white males)	6	0.84
	Acetone (white males)	5	0.86
	Isopropanol (white males)	27	0.64
	Isopropanol (black males)	2	0.56

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Malker and Gemne, 1987	Swedish printing-industry workers, employed in 1960		
	Males	190	1.5 (1.2–1.7)[b]
	Females	9	1.3
Engholm and Englund, 1982	Male members of the Swedish Painters Union		
	Years since entry into the union		
	≥0	81	1.28 (p <0.05)
	≥5	75	1.24 (p <0.05)
	≥10	74	1.31 (p <0.05)
	≥15	66	1.28 (p <0.05)
	≥20	58	1.26 (p <0.05)
	≥25	51	1.32 (p <0.05)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Potential routine exposure to mixed solvents	221	0.88 (0.77–1.01)
Steenland and Palu, 1999	Members of US painters unions		
	Total cohort	1746	1.23 (1.17–1.29)
	20 years since first union membership	1360	1.24 (1.18–1.31)
Greenland et al., 1994	White male transformer-assembly workers, ever exposed	NA	1.57 (1.08–2.27)
Acquavella et al., 1993	Metal-components manufacturing workers		
	Solvents, ever exposed	4	1.9 (0.5–4.9)
Walker et al., 1993	Shoe-manufacturing workers in Ohio, employed >1 month		
	Total cohort	99	1.47 (1.20–1.80)
	Males	68	1.56 (1.22–1.99)
	Females	31	1.30 (0.89–1.86)
Teta et al., 1992	Male ethanol and isopropanol production workers		
	South Charleston SC plant		
	All workers, ever employed	14	0.87 (0.5–1.5)
	Workers in exposed unit ≥ 10 years	2	0.56
	Texas City, TX plant		
	All workers, ever employed	8	1.10 (0.5–2.2)
	Workers in exposed unit ≥10 years	1	NA
Matanoski et al., 1986	US painters and allied tradesmen		
	Total cohort	448	1.06 (0.96–1.16)
Stockwell and Matanoski, 1985	Male construction and maintenance painters in New York		
	Usual occupation of painter	51	2.75 (1.45–5.21)
Engholm and Englund, 1982	Male members of the Swedish Painters Union		
	Years since entry into the union:		
	≥0	124	1.27 (p <0.05)
	≥5	118	1.25 (p <0.05)
	≥10	114	1.28 (p <0.05)
	≥15	103	1.27 (p <0.05)
	≥20	92	1.26 (p <0.05)
	≥25	80	1.27 (p <0.05)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Morgan et al., 1981	Male US paint or varnish manufacturing workers		
	Solvents excluding lacquer, 1+ years of exposure	51	1.14
Waxweiler et al., 1981	Male synthetic-chemical plant workers, ever employed	42	1.49 (1.08–2.03)[a]
Alderson and Rattan, 1980	Male workers at dewaxing plants in the UK, employed >1 year		
	Workers in isopropanol alcohol plant	2	0.78 (0.09–2.81)[a]
	Workers in methyl ethyl ketone plant	1	0.17 (0.00–0.93)[a]
Englund, 1980	Male Swedish painters, ever certified or union member	124	1.27 (1.06–1.52)[a]
Case–Control Study			
Brownson et al., 1993	Occupational exposure among females in Missouri—Printing industry		
	Lifetime nonsmokers	6	0.8 (0.3–2.0)
	Exposure range		
	Low: ≤8 years	NA	0.6 (0.2–2.2)
	High: >8 years	NA	1.3 (0.5–3.7)

NOTE: NA = not available; U-TCA = urinary metabolite of trichloroethylene.
[a]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.
[b]99% confidence limits.

BONE CANCER

Epidemiologic Studies of Exposure to Organic Solvents and Bone Cancer

Blair and colleagues (1998) extended the followup of a cohort of aircraft-manufacturing workers (Spirtas et al., 1991) that used a detailed exposure-assessment method. An increased bone cancer risk was reported after adjustment for age, calendar time, and sex (RR = 2.1, 95% CI = 0.2–18.8) in workers exposed to trichloroethylene.

One study assessed whether an association existed between exposure to benzene and bone cancer. To evaluate the specific relationship between exposure to benzene and cancer risk, Wong (1987a) examined mortality among workers employed in seven chemical-manufacturing plants. An increased relative risk of bone cancer was found in the exposed group of workers (SMR = 3.17, 95% CI = 0.38–11.46). Wong (1987b) also estimated exposure to benzene in terms of 8-hour TWAs and peak levels of exposure and found that the relative risk of bone cancer increased with duration of exposure (SMR = 6.63; one exposed case). Those results were inconclusive for an association because of the very small number of exposed cases, which resulted in highly variable risk estimates.

Fu and colleagues (1996) examined two historical cohorts of shoe workers in England and Florence, Italy, and used job titles to assess cancer mortality in relation to exposure to leather dusts and solvents. A slight increase in bone cancer was observed in the English cohort among those with probable solvent exposure (SMR = 1.12, 95% CI = 0.03–6.26), and no cases of bone cancer were reported in the Florence cohort. The committee reviewed the study by Nielsen and colleagues (1996) in which the risk of bone cancer in a cohort of lithographers was examined. Only one exposed case was observed (SIR = 11.4, 95% CI = 0.6–56.0).

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Summary and Conclusion

The relationship between exposure to organic solvents and bone cancer was reported in only four cohort studies, representing three different solvent exposures. Each study had low power, and exposure assessment relied primarily on job titles as surrogates of exposure. No case–control studies of bone cancer were identified. Studies with larger numbers of exposed cases (increased power) and more precise exposure assessment are needed for the committee to evaluate the relationship between solvent exposures and risk of bone cancer. Table 6.16 identifies the key studies and relevant data points reviewed by the committee in drawing its conclusion. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and bone cancer.

TABLE 6.16 Selected Epidemiologic Studies—Bone Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Mortality			
Blair et al., 1998	Aircraft maintenance workers in Utah, employed in exposed area >1 year	5	2.1 (0.2–18.8)
Benzene			
Cohort Study—Mortality			
Wong, 1987a,b	Male Chemical Manufacturers Association workers		
	Continuous exposure	2	3.17 (0.38–11.46)
	Duration of exposure		
	<5 years	1	2.63
	5–14 years	1	6.63
	≥15 years	0	—
Unspecified Mixtures of Organic Solvents			
Cohort Study—Incidence			
Nielsen et al., 1996	Danish lithographers, ever employed	1	11.4 (0.6–56.0)
Cohort Study—Mortality			
Fu et al., 1996	Shoe-manufacturing workers		
	English cohort, employed in 1939	6	2.08 (0.76–4.52)
	Probable solvent based on work area	1	1.12 (0.03–6.26)
	Florence cohort, ever employed	0	0 (0.0–3.45)

SOFT TISSUE SARCOMA

Because of the lack of available studies on the relationship between exposure to organic solvents and soft tissue sarcomas (STS), a conclusion regarding association could not be drawn. Only one study (Serraino et al., 1992) identified by the committee analyzed the relationship between relevant exposures reviewed in this report ("benzene/solvents" and "dyes/paints") and STS. Although the population-based case–control study observed an increased risk of STS among men exposed to "benzene/solvents" for more than 10 years (OR = 2.2, 95% CI = 0.9–5.5), the study was limited by the use of self-reported exposures. Additional studies are needed to support the relationship before a conclusion regarding association can be drawn.

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SKIN CANCER

Description of Case–Control Studies

Table 6.17 identifies the study characteristics of two papers from the Montreal multisite cancer case–control study on the association between exposure to specific organic solvents and solvent mixtures and the risk of melanoma. The study was designed so that in-person interviews were used mostly, and telephone interviews or self-administered questionnaires were limited to next of kin or hard-to-interview subjects. The interviews included a job-specific module to obtain detailed information on each job that a subject held in the entire working history, such as dates of employment, the employer's activities and products, job tasks, and work environment. Using the job-history information, a team of industrial hygienists and chemists estimated exposures to about 300 of the most common occupational agents. The study population was used for exposure-specific and cancer-specific studies. Fritschi and Siemiatycki (1996a) evaluated the relationship between melanoma and exposure to 85 chemical substances, 13 occupations, and 20 industries. The same set of cases was studied by Gérin and colleagues (1998) in relation to occupational exposure to the hydrocarbons benzene, toluene, xylene, and styrene.

Epidemiologic Studies of Exposure to Organic Solvents

No increase in melanoma mortality was found among two cohorts of aircraft-maintenance workers (Blair et al., 1998; Boice et al., 1999), a cohort of workers monitored for a metabolite of trichloroethylene (Hansen et al., 2001), or a cohort of uranium-processing workers (Ritz, 1999). An increased risk of melanoma (for "any exposure," OR = 3.6, 95% CI = 1.5–9.1) was found in a case–control study in Montreal (Fritschi and Siemiatycki, 1996a). Two studies of workers monitored for exposure to trichloroethylene found mixed results for nonmelanoma skin cancers (Axelson et al., 1994; Hansen et al., 2001). The studies were based on small numbers of exposed cases and did not control for exposure to sunlight, an important confounding variable.

Two studies of tetrachloroethylene-exposed workers, one in aircraft manufacturing (Boice et al., 1999) and one of dry-cleaning workers (Blair et al., 1990), showed no association between exposure and skin cancer risk. Boice and colleagues examined melanoma specifically, and Blair and colleagues looked at all skin cancers combined.

Several other solvents thought to have been used in the Gulf War—including methylene chloride, benzene, toluene, xylene, and phenol—were investigated in relation to melanoma. The committee identified only one relevant epidemiologic study for each substance. A cohort study of cellulose-fiber production workers showed an increased risk of melanoma mortality (SMR = 1.94 95% CI = 0.24–7.00) (Lanes et al., 1993). No increased risks were reported for melanoma and exposure to benzene, toluene, or xylene (Gérin et al., 1998) or for any type of skin cancer and exposure to phenol (Dosemeci et al., 1991).

Melanoma was not found to be associated with exposure to unspecified mixtures of solvents, as reported in several occupational studies (Anttila et al., 1995; Berlin et al., 1995; Boice et al., 1999; Bourguet et al., 1987; Fritschi and Siemiatycki, 1996a). The findings on risk of nonmelanoma skin cancer and unspecified mixtures of solvents were inconsistent but tended to be negative. Studies that found positive associations were variable and based on few exposed cases, and sunlight exposure was not controlled for.

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TABLE 6.17 Description of Case–Control Studies of Melanoma Skin Cancers and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Fritschi and Siemiatycki, 1996a	Male cases and controls, age 35–70 years, diagnosed in 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed for one of 19 anatomic cancer sites; age-matched, population-based controls were also chosen from electoral lists and RDD (see also Gérin et al., 1998) Response rates: 83% of all cases, 71% of population controls	103 melanoma	1,066 subjects for each site, consisting of 533 population controls and 533 randomly selected subjects from the eligible cancer control group	Trichloroethylene Solvents	In-person interviews with segments on work histories (job titles); exposures attributed by a team of chemists and industrial hygienists	Unconditional logistic regression	Age, years of schooling, ethnicity
Gérin et al., 1998	Male cases and controls, age 35–70 years, diagnosed in 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed for one of 19 anatomic cancer sites; age-matched, population-based controls were also chosen from electoral lists and RDD (see also Fritschi and Siemiatycki, 1996a) Response rates: 82% of all cases, 71% of population controls	103 melanoma	1,066 subjects for each site, consisting of 533 population controls and 533 randomly selected subjects from the eligible cancer control group	Benzene Toluene Xylene	In-person interviews with segments on work histories (job titles); exposures attributed by a team of chemists and industrial hygienists	Unconditional logistic regression	Age, family income, ethnicity, cigarette smoking, respondent status

NOTE: RDD = random-digit dialing

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Summary and Conclusion

Several studies of specific and mixed solvents examined the role of exposure and the risk of skin cancer, specifically melanoma and nonmelanoma. However, small numbers of exposed cases and the lack of validated exposure assessment were limitations of the studies. Almost all studies on specific organic solvents and unspecified mixtures of organic solvents found no association between exposure and incidence or mortality from melanoma, nonmelanoma skin cancer, or skin cancer in general. Several studies used biologic monitoring to assess exposure (e.g., Anttila et al., 1995; Axelson et al., 1994; Hansen et al., 2001), but the inability of most studies to control for well-established risk factors of skin cancer—such as age, ethnicity, geography, presence of nevi, and time spent in the sun—limits the validity of their findings. Tables 6.18–19 identify the key studies and relevant data points reviewed by the committee in drawing its conclusions. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure solvents under review and melanoma or nonmelanoma skin cancer.

TABLE 6.18 Selected Epidemiologic Studies—Melanoma Skin Cancers and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored male Danish workers	2	0.9 (0.1–3.4)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers, ever exposed	2	0.46 (0.06–1.67)
Ritz, 1999	White male uranium-processing workers, ever exposed		
	Melanoma and nonmelanoma	4	0.64 (0.17–1.63)
Blair et al., 1998	Aircraft-maintenance workers, ever exposed	9	1.0 (0.3–3.1)
Case–Control Study			
Fritschi and Siemiatycki, 1996a	Male residents of Montreal, Canada		
	Any exposure	8	3.6 (1.5–9.1)
	Substantial exposure	4	3.4 (1.0–12.3)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers, ever exposed	2	0.95 (0.12–3.43)
Blair et al., 1990	Dry-cleaning union members in Missouri, ever employed		
	Melanoma and nonmelanoma	2	0.8 (0.1–2.8)
Other Specific Organic Solvents			
Cohort Studies—Mortality			
Lanes et al., 1993	Cellulose-fiber production workers in South Carolina, exposed to methylene chloride	2	1.94 (0.24–7.00)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Dosemeci et al., 1991	Male US industrial workers, ever exposed to phenol		
	Melanoma and nonmelanoma	7	0.9 (0.4–1.8)
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada, any exposure		
	Benzene	11	0.6 (0.3–1.2)
	Toluene	5	0.4 (0.1–0.9)
	Xylene	3	0.3 (0.1–0.8)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Workers in Finland biologically monitored for halogenated hydrocarbons	5	0.71 (0.23–1.66)
Berlin et al., 1995	Patients with solvent-related disorders, ever exposed	3	0.7 (0.1–2.0)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers, ever exposed		
	Mixed solvents	10	0.87 (0.42–1.60)
Morgan et al., 1981	Male paint and coatings manufacturing workers, ever employed		
	Melanoma and nonmelanoma	4	1.48
Case–Control Study			
Fritschi and Siemiatycki, 1996a	Male residents of Montreal, Canada, ever exposed		
	Solvents	33	0.8 (0.5–1.3)

TABLE 6.19 Selected Epidemiologic Studies—Nonmelanoma Skin Cancers and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored male Danish workers	15	1.0 (0.6–1.6)
Cohort Studies—Mortality			
Ritz, 1999	White male uranium-processing workers, ever exposed		
	Melanoma and nonmelanoma	4	0.64 (0.17–1.63)
Axelson et al., 1994	Biologically monitored male Swedish workers		
	Nonmelanoma	8	2.36 (1.02–4.65)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Mortality			
Blair et al., 1990	Dry-cleaning union members in Missouri, ever employed		
	Melanoma and nonmelanoma	2	0.8 (0.1–2.8)
Other Specific Organic Solvents			
Cohort Study—Mortality			
Dosemeci et al., 1991	Male US industrial workers, ever exposed to phenol		
	Melanoma and nonmelanoma	7	0.9 (0.4–1.8)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1995	Workers in Finland biologically monitored for halogenated hydrocarbons	2	0.46 (0.06–1.67)
Berlin et al., 1995	Patients with solvent-related disorders, ever exposed	4	1.5 (0.4–4.0)
Bourguet et al., 1987	Male tire and rubber manufacturing workers, ever exposed		
	Low solvent exposure	15	0.6
	Medium solvent exposure	7	1.1
	High solvent exposure	34	1.1
Cohort Study—Mortality			
Morgan et al., 1981	Male paint and coatings manufacturing workers, ever employed		
	Melanoma and nonmelanoma	4	1.48

BREAST CANCER

Description of Case–Control Studies

All breast cancer case–control studies were population-based and are identified in Table 6.20 below. Aschengrau and colleagues (1998) evaluated the relationship between the risk of breast cancer and exposure to tetrachloroethylene in drinking water, which was estimated on the basis of an algorithm that accounted for residential history, water flow, and pipe characteristics, as established by Webler and Brown (1993). Three other case–control studies evaluated breast cancer risk and occupational exposure (Band et al., 2000; Hansen, 1999; Petralia et al., 1999). Each of the studies ascertained exposure differently: through use of occupational titles (Band et al., 2000), through linkage of pension-fund occupational-history information with solvent use in industries (Hansen, 1999), and through interviews with subjects to obtain occupational histories, which were linked with job–exposure matrixes to assign cumulative exposure measures (Petralia et al., 1999). Potential confounding variables were handled adequately in three of the four studies (Aschengrau et al., 1998; Band et al., 2000; Petralia et al., 1999).

Epidemiologic Studies of Exposure to Organic Solvents and Breast Cancer

Risk of breast cancer was not increased in two Scandinavian studies of biologically monitored workers exposed to trichloroethylene (Anttila et al., 1995; Hansen et al., 2001). Among women exposed to trichloroethylene as aircraft-maintenance workers, Blair and colleagues (1998) found a risk of breast cancer associated with any exposure to trichloroethylene (SMR = 1.8, 95% CI = 0.9–3.3) and more than a 3-fold risk associated with continuous low exposure to trichloroethylene (SMR = 3.4, 95% CI = 1.4–8.0). Other cohort studies of aircraft workers in which trichloroethylene was considered a predominant solvent did not report increased mortality rates from breast cancer (male and female combined) (Boice et al., 1999; Morgan et al., 1998).

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TABLE 6.20 Description of Case–Control Studies of Breast Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Aschengrau et al., 1998	Female cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from the records of HCFA and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 79% of cases, 76% of HCFA controls, 74% of RDD controls, 79% of next of kin of deceased controls	258	686	Tetrachloroethylene	Relative delivered dose estimated in model accounting for location and years of residence, water flow, pipe characteristics	Multiple logistic regression	Age at diagnosis, vital status, family and personal history of breast cancer or disease, age at first birth, occupational exposure to solvents
Petralia et al., 1999	Female cases, age 40 years or more, identified through major hospitals in two New York counties in 1986–1991, with histologic confirmation; controls randomly selected from lists of the NY State Department of Motor Vehicles, matched for age and county Participation rates: 66% of cases, 62% of controls	301	316	Benzene	In-person interviews to assess lifetime occupational history; occupations and industries coded; assigned potential exposures to polycyclic aromatic hydrocarbons through use of a job–exposure matrix	Unconditional logistic regression	Age, years of education, age at first birth, age at menarche, history of benign breast disease, family breast cancer history, Quetelet index, months of lactation
Hansen, 1999	Female cases, identified through the Danish Cancer Registry, born in 1934–1969 with diagnosis in 1970–1989; controls randomly selected from the central population register, matched for year of birth and sex	7,802	7,802	Industries with extensive solvent use	Past employment determined through linkage to the national pension fund files; occupations from five industrial groupings (except administrative jobs) classified as exposed to solvents	Conditional logistic regression	Age, social class, age at first child, number of children

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Band et al., 2000	Female cases, under 75 years old, identified through the British Columbia Cancer Registry as Canadian citizens residing in British Columbia and diagnosed in 1988–1989, with histologic confirmation; controls selected from voter list, matched for age Response rates: 74.7% of cases, 76.1% of controls	995	1020	Laundering and dry-cleaning (occupation and industry)	Mailed questionnaire to assess lifetime job history with occupational and industry coding	Conditional logistic regression	Ethnicity, age at menarche and menopause, smoking, marital status, education, alcohol consumption, other medical factors

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing..

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Some epidemiologic studies have either specifically addressed exposure to tetrachloroethylene or examined the effect of dry-cleaning work in relation to breast cancer risk. Aschengrau and colleagues (1998) conducted a case–control study in the Cape Cod area where drinking water was contaminated with tetrachloroethylene. Increased risks of breast cancer were found with longer latency. Excluding exposures occurring within the 9 years before diagnosis, the adjusted relative risks of breast cancer increased with increasing exposure (exposure greater than the 90th percentile: OR = 7.8, 95% CI = 0.9–167.0). A study of aircraft-manufacturing workers showed a slight increase in mortality from breast cancer with potential routine exposure to tetrachloroethylene (SMR = 1.16, 95% CI = 0.32–2.97) (Boice et al., 1999). A cohort of dry-cleaning union members showed no increase in breast cancer mortality (SMR = 0.91, 95% CI = 0.55–1.40) or in workers exposed only to tetrachloroethylene (SMR = 0.78, 95% CI = 0.28–1.69) (Ruder et al., 2001).

Band and colleagues (2000) examined the potential risk of premenopausal and postmenopausal breast cancer in multiple occupations in British Columbia. Increased risk of breast cancer was observed in women reporting any or usual work in laundry and dry-cleaning. Exposure to tetrachloroethylene and other solvents was based on an occupational title of "laundering/dry-cleaning" for premenopausal women and dry-cleaning occupational and industry titles for postmenopausal women. Among numerous positive associations, postmenopausal women experienced an almost 5-fold risk if their usual occupation was laundry and dry-cleaning (OR = 4.85, 95% CI = 1.26–18.7). The other cohort studies of dry cleaners did not show positive associations between this employment and breast cancer risk in women (Blair et al., 1990).

The association between exposure to benzene and the risk of breast cancer was assessed in two cohort studies and one case–control study. Petralia and colleagues (1999) reported an increased adjusted risk of premenopausal breast cancer with exposure to benzene and that risk increased with probability and duration of exposure (duration at least 4 years: OR = 3.38, 95% CI = 1.25–9.17). The large cohort study of Chinese benzene-exposed workers did not show an increase in breast cancer mortality (RR = 0.9, 95% CI = 0.3–3.2) (Yin et al., 1996a). The Danish cohort study, in which exposure was assessed using pension-fund records of job history, showed an increased incidence of breast cancer in men (OR = 2.2, 95% CI = 1.4–3.6) (Hansen, 2000).

The cohort of aircraft-maintenance workers studied by Blair and colleagues experienced an increased risk of breast cancer with exposure to methylene chloride (RR = 3.0, 95% CI = 1.0–8.8). The study also produced increased relative risks of breast cancer with exposure to several specific solvents; positive associations with 1,1,1-trichloroethane, acetone, isopropyl alcohol, toluene, and methyl ethyl ketone were found.

Employees of a cellulose-fiber production plant with heavy methylene chloride use did not experience a rate of breast cancer higher than that in the local county population (SMR = 0.54, 95% CI = 0.11–1.57) (Lanes et al., 1993).

Several studies examined the potential relationship between breast cancer risk and exposure to mixtures of solvents (Anttila et al., 1995, 1998; Berlin et al., 1995; Blair et al., 1998; Cocco et al., 1998; Hansen, 1999, Shannon et al., 1988; Weiderpass et al., 1999). The studies characterized the exposure in general terms, such as "organic solvents" or "mixed solvents." In two instances (Anttila et al., 1995, 1998), specific constituent solvents were mentioned, but separate analyses were not performed. Hansen (1999) found increased risks of breast cancer (predominantly premenopausal) associated with occupations and industries with heavy solvent use (over 10 years of employment: OR = 1.31, 95% CI = 1.01–1.75). In a cohort study of lamp manufacturers, Shannon and colleagues (1998) found a 2-fold risk of breast cancer in solvent-

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exposed workers in coiling and wire drawing. An association with any exposure to solvents was found among aircraft-maintenance workers (SMR = 1.6, 95% CI = 0.9–2.8) (Blair et al., 1998). No associations were found in studies of workers exposed to aromatic or halogenated solvents (Anttila et al., 1995, 1998), in patients with solvent-related disorders (Berlin et al., 1995), and in aircraft-manufacturing workers (Garabrant et al., 1988).

Summary and Conclusion

In most occupational settings, multiple solvent exposures occurred, so exposures to specific solvents may be highly correlated. Because many studies used occupational titles as exposure surrogates, the ability to assess an association between specific solvents and breast cancer risk was compromised.

A number of studies assessed breast cancer risk and solvent exposure in general, and others provided exposure estimates for specific individual solvents, such as trichloroethylene, tetrachloroethylene, dry-cleaning solvents, benzene, and methylene chloride. The evidence was limited by nonspecific exposure assessments and a reliance on mortality from breast cancer. Nondifferential misclassification of exposure, poor control for confounding, and low statistical power due to small numbers were additional limitations. Table 6.21 identifies the key studies and relevant data points reviewed by the committee in drawing its conclusion. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and breast cancer.

TABLE 6.21 Selected Epidemiologic Studies—Breast Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored workers in Denmark		
	Females, ever exposed	4	0.9 (0.2–2.3)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Potential routine exposure	7	1.31 (0.53–2.69)
Blair et al., 1998	Aircraft-maintenance workers in Utah (females)		
	Any exposure	20	1.8 (0.9–3.3)
	Low, continuous	8	3.4 (1.4–8.0)
	Frequent peaks	10	1.4 (0.7–3.2)
Morgan et al., 1998	Aerospace workers in Arizona		
	Ever exposed	16	0.75 (0.43–1.22)
	Low exposure	11	1.03 (0.51–1.84)
	High exposure	5	0.47 (0.15–1.11)
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons	34	0.85 (0.59–1.18)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	US dry-cleaning workers		
	Dry-cleaning, employed >1 year	20	0.91 (0.55–1.40)
	Tetrachloroethylene only	6	0.78 (0.28–1.69)
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Potential routine exposure	4	1.16 (0.32–2.97)
Blair et al., 1990	Dry-cleaning union members in Missouri (females)	36	1.0 (0.7–1.4)
Case–Control Studies			
Band et al., 2000	Female cases from the British Columbia Cancer Registry		
	Premenopausal		
	Laundering or dry-cleaning (occupation)		
	Usual exposure	1	—
	Ever exposed	4	1.77 (0.41–7.72)
	Postmenopausal		
	Laundry or dry-cleaning (occupation)		
	Usual exposure	8	4.85 (1.26–18.7)
	Ever exposed	8	1.33 (0.55–3.19)
	Laundering and dry-cleaning (industry)		
	Usual exposure	9	5.24 (1.41–19.5)
	Ever exposed	12	1.42 (0.68–2.99)
	Power laundries or dry cleaners (industry)		
	Usual exposure	9	2.00 (0.78–5.13)
	Ever exposed	21	1.67 (0.89–3.13)
Aschengrau et al., 1998	Residents of upper Cape Cod, MA		
	Postmenopausal women		
	75th percentile (9-year latency)	NA	3.4 (0.7–19.1)
	90th percentile (9-year latency)	NA	7.8 (0.9–167.0)
Benzene			
Cohort Study—Incidence			
Hansen, 2000	Male members of the national pension fund in Denmark		
	No lag time	19	2.2 (1.4–3.6)
	>10 years lag	12	2.5 (1.3–4.5)
Cohort Study—Mortality			
Yin et al., 1996a	Chinese factory workers (females), ever exposed	8	0.9 (0.3–3.2)
Case–Control Study			
Petralia et al., 1999	Female residents of New York state		
	Any exposure	56	1.91 (1.18–3.08)
	Duration <4 years	8	0.80 (0.30–2.16)
	Duration ≥4 years	16	3.38 (1.25–9.17)
	Low probability	8	1.22 (0.42–3.56)
	Medium or high probability	16	2.14 (0.89–5.12)
	Low intensity	16	2.38 (0.97–5.87)
	Medium or high intensity	8	1.07 (0.37–3.07)
	Low cumulative	13	1.43 (0.59–3.47)
	Medium or high cumulative	11	2.21 (0.77–6.36)
	10 to 19 year latency	5	1.23 (0.34–4.46)
	≥20 year latency	16	2.09 (0.85–5.14)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Methylene Chloride			
Cohort Studies—Mortality			
Blair et al., 1998	Aircraft-maintenance workers in Utah, ever exposed (females)	4	3.0 (1.0–8.8)
Lanes et al., 1993	Cellulose-fiber production-plant workers in South Carolina, employed >3 months	3	0.54 (0.11–1.57)
Other Specific Organic Solvents			
Cohort Study—Mortality			
Blair et al., 1998	Aircraft-maintenance workers in Utah, employed >1 year (females)		
	1,1,1-Trichloroethane	3	3.3 (1.0–11.2)
	Acetone	7	1.9 (0.8–4.6)
	Isopropyl alcohol	8	3.7 (1.6–8.4)
	Methyl ethyl ketone	8	2.1 (0.9–4.7)
	Stoddard solvent	15	1.2 (0.6–2.4)
	Toluene	10	2.0 (0.9–4.2)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons	15	0.79 (0.44–1.30)
	Latency 0–9 years	8	0.61 (0.26–1.21)
	Latency 10+ years	7	1.18 (0.47–2.42)
Anttila et al., 1995	Finnish workers biologically monitored for exposure to halogenated hydrocarbons	34	0.85 (0.6–1.2)
	Latency 0–9 years	12	0.84 (0.4–1.5)
	Latency 10+ years	22	0.85 (0.5–1.3)
Berlin et al., 1995	Swedish patients with solvent-related disorders (females)	3	1.1 (0.2–3.2)
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years	16	0.91 (0.52–1.48)
Shannon et al., 1988	Lamp manufacturing workers, employed >6 months		
	Coiling or wire drawing	8	2.04 (0.88–4.02)
Cohort Study—Mortality			
Blair et al., 1998	Aircraft-maintenance workers in Utah (females)		
	Organic solvents, ever exposed	28	1.6 (0.9–2.8)
Case–Control Studies			
Hansen, 1999	Danish women employed in industries with heavy solvent use		
	Employed ≥1 year, no lag	743	1.27 (1.13–1.43)
	Employed ≥1 year, ≥15 years lag	472	1.43 (1.24–1.67)
	Employed >10 years, no lag	113	1.31 (1.01–1.75)
	Employed >10 years, ≥15 years lag	97	1.97 (1.39–2.79)
Cocco et al. 1998	Male breast cancer cases from National Mortality Follow-Back Survey exposed to organic solvents		
	Low probability	26	0.8 (0.5–1.3)
	Medium probability	15	0.9 (0.5–1.6)
	High probability	1	0.5 (0.1–4.3)
	Low intensity	18	0.8 (0.4–1.4)
	Medium intensity	20	0.8 (0.5–1.5)
	High intensity	4	0.7 (0.2–1.2)

NOTE: NA = not available.

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FEMALE REPRODUCTIVE CANCERS

Epidemiologic Studies of Exposure to Organic Solvents and Cervical Cancer

Anttila and colleagues (1995) conducted a followup study of cancer incidence among Finnish workers who were biologically monitored for exposure to trichloroethylene and other halogenated hydrocarbons. An increased risk of cervical cancer was observed among women with any exposure to trichloroethylene (SIR = 2.42, 95% CI = 1.05–4.77), and the relative risks increased with increasing exposure (RR_{low} = 1.86, 95% CI = 0.38–5.45; RR_{high} = 4.35, 95% CI = 1.41–10.1). A similar biomonitoring study in Denmark showed a 3.8-fold risk of cervical cancer (SIR = 3.8, 95% CI = 1.0–9.8) (Hansen et al., 2001), but no exposure–response pattern was reported.

A retrospective cohort study by Blair and colleagues (1998) of US civilians employed in aircraft maintenance showed increased mortality from cervical cancer (SMR = 3.0, 95% CI = 0.5–6.5); the relative risk was increased among women with high cumulative exposure (SMR = 3.0, 95% CI = 0.8–11.7). Two studies of aerospace and aircraft-manufacturing workers (Boice et al., 1999; Morgan et al., 1998) found no deaths from cervical cancer.

Only two studies specifically examined the association between exposure to tetrachloroethylene and cervical cancer. However, given that tetrachloroethylene is often used in dry-cleaning work, studies on laundry and dry-cleaning workers were also reviewed.

Boice and colleagues (1999) did not observe any cases of cervical cancer among women exposed to tetrachloroethylene. The biomonitoring study of tetrachloroethylene-exposed workers by Anttila and colleagues (1995) found an increased risk of cervical cancer (SIR = 3.20, 95% CI = 0.39–11.6).

Ruder and colleagues (2001) found an increased risk of cervical cancer (SMR = 1.95, 95% CI = 1.00–3.40) among members of a dry-cleaning union representing four areas in the United States, and Blair and colleagues (1990) estimated an SMR of 1.7 (95% CI = 1.0–2.0) in a study of dry-cleaning union members in Missouri. Ruder and colleagues (2001) found that the risk of cervical cancer increased further among women who were exposed for more than 5 years (SMR = 2.78 for less than 20 years of latency and 2.40 for 20 years or more of latency), but Blair and colleagues (1990) found no increases in risk with increasing exposure.

The available evidence concerning an association between exposure to methylene chloride and risk of cervical cancer was sparse. Gibbs and colleagues (1996) examined the risk of cervical cancer among women employed in cellulose-fiber production. They found an increased risk of cervical cancer among workers with low or high exposure (SMR_{low} = 2.96, 95% CI = 0.96–6.92; SMR_{high} = 5.40, 95% CI = 0.14–30.1), but it was also increased in workers with no measured exposure to methylene chloride (SMR = 7.02, 95% CI = 0.18–39.1). Shannon and colleagues (1988) studied lamp manufacturing workers who were exposed to methylene chloride and other solvents and substances used during the manufacturing process, particularly coiling and wire drawing, and found no increased risk of cervical cancer.

The study of aircraft-manufacturing workers by Boice and colleagues (1999) did not show any cases of cervical cancer in women exposed to mixtures of solvents. In 1995, Berlin and colleagues examined cancer incidence and mortality patterns among patients with suspected solvent-related disorders and found that the incidence of cervical cancer was high (SIR = 3.7, 95% CI = 2.2–6.2).

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Summary and Conclusion

A limited number of papers were found that reported the risk of cervical cancer in connection with exposure to specific solvents. There were no case–control studies, and most of the cohort studies had very few cases. The studies of cervical cancer and specific solvent exposures did not provide evidence of an association between most of the specific solvents or solvent mixtures except for trichloroethylene.

For exposure to trichloroethylene and cervical cancer, three cohort studies showed an increased risk of cervical cancer with exposure to trichloroethylene, and two other studies did not have sufficient numbers or followup to find any deaths. An exposure–response relationship for the highest exposure was reported in two of the biologic monitoring studies (Anttila et al., 1995; Blair et al., 1998). Some committee members believed that the evidence of an association between cervical cancer and exposure to trichloroethylene should be classified as limited/suggestive. However, some committee members were concerned about confounding by socioeconomic status and the increased risk of exposure to the human papilloma virus (HPV), which is associated with the development of cervical cancer (NCI, 2002). The studies compared the risk of cervical cancer among unskilled workers of low socioeconomic status in Scandinavian countries with that of the general population. The positive associations could have been attributed to the lack of control for socioeconomic status or HPV infection. Moreover, no trends were seen with duration of employment or cumulative exposure in the other biologically monitored study of Danish workers (Hansen et al., 2001). There was also a concern that the numbers of studies and exposed cases were too small to support a conclusion that the evidence was limited/suggestive. In addition, three studies (Blair et al., 1998; Boice et al., 1999; Morgan et al., 1998) had no exposed cases, although cases of cervical cancer were expected. Thus, some committee members concluded that the evidence was inadequate/insufficient to determine whether an association exists.

As a result, after extensive discussion, the committee could not reach a consensus as to whether the evidence was limited/suggestive of an association or was inadequate/insufficient to determine whether an association exists between cervical cancer and exposure to trichloroethylene. Future studies that control for socioeconomic status are needed to determine whether there is an association between exposure to trichloroethylene and the risk of cervical cancer.

For exposure to tetrachloroethylene and dry-cleaning solvents, although several studies were positive, exposure–response patterns were absent and limited the strength of the evidence. Only one study on the exposure to unspecified mixtures of organic solvents and risk of cervical cancer was identified. Although the finding was particularly strong, no exposure–relationship pattern was reported. Additional corroborating studies are needed before a determination can be made that an association exists between exposure to solvent mixtures and cervical cancer. Table 6.22 identifies the studies reviewed by the committee in making its conclusion regarding association.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than trichloroethylene, and cervical cancer.

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TABLE 6.22 Selected Epidemiologic Studies—Cervical Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored workers in Denmark	4	3.8 (1.0–9.8)
Anttila et al., 1995	Biologically monitored workers in Finland		
	Whole period of followup (mean individual urinew level)	8	2.42 (1.05–4.77)
	<100 μmol/L	3	1.86 (0.38–5.45)
	100+ μmol/L	5	4.35 (1.41–10.1)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	0	—
Blair et al., 1998	Aircraft-maintenance workers in Utah, ever exposed	5	1.8 (0.5–6.5)
	<5 unit-years	1	0.9 (0.1–8.3)
	5–25 unit-years	0	—
	>25 unit-years	4	3.0 (0.8–11.7)
Morgan et al., 1998	Aerospace workers in Arizona, employed >6 months	0	—
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Biologically monitored workers in Finland	2	3.20 (0.39–11.6)
Cohort Studies—Mortality			
Ruder et al., 2001	US dry-cleaning workers		
	Employed >1 year	12	1.95 (1.00–3.40)
	Employed 5+ years, <20 years of latency	4	2.78 (0.75–7.71)
	Employed 5+ years, ≥20 years of latency	3	2.40 (0.48–7.86)
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	0	—
Blair et al., 1990	Dry-cleaning union members in Missouri	21	1.7 (1.0–2.0)
Methylene Chloride			
Cohort Studies—Mortality			
Gibbs et al., 1996	Cellulose triacetate-fiber workers, employed >3 months		
	Methylene chloride, no exposure	1	7.02 (0.18–39.1)
	Methylene chloride, low probability	5	2.96 (0.96–6.92)
	Methylene chloride, high probability	1	5.40 (0.14–30.1)
Shannon et al., 1988	Lamp-manufacturing workers (primary exposure to methylene chloride), employed >6 months	1	1.05 (0.03–5.86)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, potential routine exposure	0	—
Berlin et al., 1995	Swedish patients with solvent-related disorders	14	3.7 (2.2–6.2)

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Epidemiologic Studies of Exposure to Organic Solvents and Ovarian and Uterine Cancer

There was a paucity of studies regarding exposure to specific solvents and ovarian or uterine cancer. No studies showed meaningful increases in the risk of uterine or ovarian cancer in relation to exposure to trichloroethylene. The number of exposed subjects was extremely small in these studies, so the data are not informative in drawing a conclusion regarding association. There were no reports of an association between risk of uterine or ovarian cancer and exposure to methylene chloride or of an association between ovarian cancer and exposure to unspecified mixtures of organic solvents (Boice et al., 1999).

Summary and Conclusion

A limited body of evidence was available for the committee to review concerning specific and unspecified solvent exposure and risk of ovarian or uterine cancer. Very few studies had sufficient power to permit meaningful analyses. Tables 6.23 and 6.24 identify the key studies reviewed by the committee in drawing its conclusions regarding various solvent exposures and ovarian or uterine cancer.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and ovarian or uterine cancer.

TABLE 6.23 Selected Epidemiologic Studies—Ovarian Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored workers in Denmark	2	2.1 (0.2–7.6)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	1	0.58 (0.01–3.22)
Morgan et al., 1988	Aerospace workers in Arizona, employed >6 months		
	Ever exposed	8	1.21 (0.52–2.38)
	Low exposure	2	0.61 (0.07–2.21)
	High exposure	6	1.79 (0.66–3.88)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	0	—
Methylene Chloride			
Cohort Study—Mortality			
Shannon et al., 1988	Lamp-manufacturing workers (primary exposure to methylene chloride), employed >6 months	1	1.47 (0.04–8.19)
Unspecified Mixtures of Organic Solvents			
Cohort Study—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, potential routine exposure	2	0.57 (0.07–2.07)

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TABLE 6.24 Selected Epidemiologic Studies—Uterine and Endometrial Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene—Uterine			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored workers in Denmark	1	1.0 (0.01–5.4)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	1	0.64 (0.02–3.57)
Morgan et al., 1988	Aerospace workers in Arizona, ever exposed	1	0.16 (0.00–0.91)
Tetrachloroethylene and Dry-cleaning Solvents—Uterine			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	0	—
Blair et al., 1990	Dry-cleaning union members in Missouri	8	1.0 (0.4–2.0)
Methylene Chloride—Uterine/Endometrial			
Cohort Studies—Mortality			
Shannon et al., 1988	Lamp-manufacturing workers (primary exposure to methylene chloride), employed >6 months	2	2.14 (0.26–7.60)
Unspecified Mixtures of Organic Solvents—Uterine			
Cohort Study—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California Mixed solvents, potential routine exposure	1	0.31 (0.01–1.71)

UROLOGIC CANCERS

Description of Case–Control Studies

The characteristics of the case–control studies considered by the committee in drawing its conclusions of association are described below for each cancer site. The principal strengths and limitations of the studies are discussed below by cancer site.

Epidemiologic Studies of Exposure to Organic Solvents and Prostate Cancer

Gérin and co-workers (1998) evaluated 15 cancer risks, including the risk of prostate cancer, related to such occupational exposures as the hydrocarbons benzene, toluene, xylene, and styrene. The study had excellent information on exposures, as assessed by in-depth interviews that were coded blindly by a team of chemists and industrial hygienists, and sufficient information on most risk factors (see Table 6.25).

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TABLE 6.25 Description of Case–Control Study of Prostate Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Gérin et al., 1998	Male cases, age 35–75 years, diagnosed in one of 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls were also chosen from electoral lists and random-digit dialing Response rates: 82% of all cases, 71% of population controls	449	1066, consisting of 533 population controls and 533 randomly selected subjects from other cases of cancer	Benzene Toluene Xylene	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures on semiquantitative scales)	Logistic regression	Age, family income, ethnicity, cigarette smoking, respondent status

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Prostate cancer mortality and incidence were not associated with exposure to trichloroethylene in the cohort studies conducted in the aircraft industry (Blair et al., 1998: SMR = 1.0, 95% CI = 0.5–2.1 for 5–25 unit-years of exposure; Boice et al., 1999: SMR = 1.03, 95% CI = 0.70–1.45). Morgan and colleagues (1998) found an excess risk of 18% (SMR = 1.18, 95% CI = 0.73–1.80), and the relative risks did not increase with increasing exposure to trichloroethylene. Other studies of occupationally exposed workers also found no association with exposure to trichloroethylene, including studies by Greenland and colleagues (1994) (OR = 0.82, 95% CI = 0.46–1.46), Hansen and colleagues (2001) (SIR = 0.6, 95% CI = 0.2–1.3), and Wilcosky and colleagues (1984) (OR = 0.62 [CI not provided by the authors, and the committee was unable to calculate it]). A cohort study of US uranium-processing workers found no increase in prostate cancer when the subjects were exposed to "light" amounts of trichloroethylene with increasing years of exposure latency (SMR ranged from 0.78–1.04). After "moderate" exposure, risk increased; the SMR ranged from 1.35 (95% CI = 0.17–10.4) after more than 2 years of exposure and no latency to 1.96 (95% CI = 0.25–15.6) after more than 5 years of exposure and a 15-year latency (Ritz, 1999).

Axelson and co-workers (1994) reported an increased risk of prostate cancer among Swedish men occupationally exposed to trichloroethylene (RR = 1.25, 95% CI = 0.84–1.84). Anttila and colleagues (1995) reported an increased risk of prostate cancer after exposure to trichloroethylene (RR = 1.38, 95% CI = 0.73–2.35).

Two cohort studies of dry-cleaning workers did not show a positive association between tetrachloroethylene and risk of prostate cancer (Blair et al., 1990: SMR = 0.7, 95% CI 0.2–1.7; Ruder et al., 1994: SMR = 0.82, 95% CI 0.33–1.69).

A German study of rotogravure printers showed no association between prostate cancer and exposure to toluene (SMR = 0.67, 95% CI = 0.13–2.66) (Wiebelt and Becker, 1999). No increased risk of prostate cancer was found in workers in Montreal who reported exposure to toluene (OR_{high} = 0.4, 95% CI = 0.1–1.4) (Gérin et al., 1998). A study of white, male rubber workers in Ohio found an association between exposure to toluene and prostate cancer (OR = 2.6) (Wilcosky et al., 1984).

Both the Montreal study and the rubber-workers study evaluated prostate cancer risk and exposure to xylene: Gérin and co-workers (1998) reported an imprecise estimate of effect of "high" exposure to xylene (OR = 1.4, 95% CI = 0.5–4.0), and Wilcosky and colleagues (1984) reported an OR of 1.5.

Gérin and colleagues also examined exposure to benzene and risk of prostate cancer. An association was found with "medium" exposure to benzene (OR = 1.7, 95% CI = 0.9–3.0) but not "high" exposure (OR = 0.9, 95% CI = 0.4–2.1).

Only one cohort study of US cellulose-fiber production workers reported exposure to methylene chloride. An increased risk of prostate cancer was found (SMR_{high} = 1.79, 95% CI = 0.95–3.06; SMR_{low} = 1.40, 95% CI = 0.64–2.66; $SMR_{no\ exposure}$ = 1.04, 95% CI = 0.22–3.05) (Gibbs et al., 1996). The magnitude of the risk increased in the high exposure group, with 20 years or more of latency (SMR = 2.08; $p < 0.05$) and with 20 years or more of exposure with 20 years of latency (SMR = 2.91; $p < 0.05$).

No increased risk of prostate cancer with exposure to unspecified mixtures of solvents was apparent in the studies the committee reviewed except one (Anttila et al., 1995). Studies that showed no increase include cohort studies by Boice and colleagues (1999) (SMR = 1.0, 95% CI 0.78–1.26), Garabrant and colleagues (1988) (SMR = 0.93,

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95% CI = 0.60–1.37), Matanoski and colleagues (1986) (SMR = 0.99, 95% CI = 0.82–1.18), Morgan and colleagues (1981) (SMR = 0.84 [CI not provided by the study authors, and the committee was unable to calculate it]), and Greenland and colleagues (1994) (OR = 0.84, 95% CI = 0.49–1.42). The cohort study by Anttila and colleagues (1995) of Finnish workers monitored for exposure to halogenated hydrocarbons showed an SIR of 1.38 (95% CI = 0.76–2.32).

Summary and Conclusion

Results of several large cohort studies of trichloroethylene exposed workers did not support an association between exposure and risk of prostate cancer, nor did the cohort studies of dry-cleaning workers. Although one positive study was identified for exposure to toluene, xylene, and benzene individually, other studies did not find an association, or the studies lacked any evidence of an exposure–response relationship. For exposure to methylene chloride, one study provided evidence for increased risk of prostate cancer with increasing years of exposure and latency, but other corroborating studies were not found. All but one of the studies on solvent mixtures found a positive association, therefore the committee was not able to determine whether an association exists between exposure and prostate cancer. Table 6.26 provides the key data points for each exposure reviewed by the committee in drawing its conclusion.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and prostate cancer.

TABLE 6.26 Selected Epidemiologic Studies—Prostate Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers, ever exposed	6	0.6 (0.2–1.3)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No exposure	61	1.0 (0.7–1.4)
	<5 unit-years	64	1.1 (0.7–1.6)
	5–25 unit-years	38	1.0 (0.6–1.6)
Anttila et al., 1995	Finnish workers monitored for exposure		
	Entire period since first measurement	13	1.38 (0.73–2.35)
	0–9 years	2	1.09 (0.13–3.91)
	10–19 years	3	0.56 (0.12–1.64)
	20+ years	8	3.57 (1.54–7.02)
Axelson et al., 1994	Swedish men occupationally exposed, trichloroethylene	26	1.25 (0.84–1.84)
Cohort Studies—Mortality			
Ritz, 1999	White male US uranium-processing workers		
	Duration of exposure, exposure lag		
	Trichloroethylene, light exposure		
	>2 years, no lag	10	0.78 (0.33–1.85)
	>2 years, 15-year lag	10	0.91 (0.38–2.18)
	>5 years, no lag	8	0.83 (0.33–2.09)
	>5 years, 15-year lag	8	1.04 (0.40–2.70)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Trichloroethylene, moderate exposure		
	>2 years, no lag	1	1.35 (0.17–10.4)
	>2 years, 15-year lag	1	1.44 (0.19–11.4)
	>5 years, no lag	1	1.58 (0.20–12.5)
	>5 years, 15-year lag	1	1.96 (0.25–15.6)
Boice et al., 1999	Aircraft-manufacturing workers in California, routine exposure	32	1.03 (0.70–1.45)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No trichloroethylene exposure	33	1.2 (0.7–2.1)
	<5 unit-years	19	0.9 (0.5–1.8)
	5–25 unit-years	13	1.0 (0.5–2.1)
Morgan et al., 1998	Aerospace workers in Arizona		
	Any exposure	21	1.18 (0.73–1.80)
	Low exposure	7	1.29 (0.52–2.66)
	High exposure	14	1.13 (0.62–1.89)
Greenland et al., 1994	White male US transformer manufacturers, ever exposed	NA	0.82 (0.46–1.46)
Wilcosky et al., 1984	White male rubber workers in Ohio, exposed >1 year	3	0.62
Tetrachloroethylene and Dry-Cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 1994	Dry-cleaning labor-union workers	7	0.82 (0.33–1.69)
Blair et al., 1990	Members of a dry-cleaning union in St. Louis, MO	5	0.7 (0.2–1.7)
Toluene			
Cohort Studies—Mortality			
Wiebelt and Becker, 1999	Male German rotogravure printers, Employed >1 year	2	0.67 (0.13–2.66)
Wilcosky et al., 1984	White male rubber workers in Ohio, exposed >1 year	3	2.6
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	51	1.0 (0.7–1.5)
	Medium exposure	17	1.3 (0.7–2.5)
	High exposure	3	0.4 (0.1–1.4)
Xylene			
Cohort Study—Mortality			
Wilcosky et al., 1984	White male rubber workers in Ohio, exposed >1 year	8	1.5
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	46	1.2 (0.8–1.8)
	Medium exposure	11	0.8 (0.4–1.7)
	High exposure	6	1.4 (0.5–4.0)
Benzene			
Cohort Study—Mortality			
Wilcosky et al., 1984	White male rubber workers in Ohio, exposed >1 year	11	0.73

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	64	1.1 (0.8–1.5)
	Medium exposure	22	1.7 (0.9–3.0)
	High exposure	9	0.9 (0.4–2.1)
Methylene Chloride			
Cohort Study—Mortality			
Gibbs et al., 1996	Cellulose-fiber production workers		
	High exposure	13	1.79 (0.95–3.06)
	≥20-year latency	NA	2.08 ($p < 0.05$)
	≥20-year latency and ≥20-year duration	NA	2.91 ($p \leq 0.05$)
	Low exposure	9	1.40 (0.64–2.66)
	No exposure	3	1.04 (0.22–3.05)
Unspecified Mixtures of Organic Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Finnish workers monitored for exposure		
	Halogenated hydrocarbons	14	1.38 (0.76–2.32)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, routine exposure	70	1.0 (0.78–1.26)
	Years exposed		
	<1	31	0.99 (0.65–1.49)
	1–4	64	0.81 (0.59–1.13)
	≥5	139	0.77 (0.58–1.02)
			p-trend = 0.06
Greenland et al., 1994	White male US transformer-assembly workers		
	Solvents, ever exposed	NA	0.84 (0.49–1.42)
Garabrant et al., 1988	Aircraft-manufacturing workers in California	25	0.93 (0.60–1.37)
Matanoski et al., 1986	US painters and allied tradesmen union members	117	0.99 (0.82–1.18)
Morgan et al., 1981	Male US paint and coatings manufacturers, employed >1 year	29	0.84

NOTE: NA = not available.

Epidemiologic Studies of Exposure to Organic Solvents and Bladder Cancer

All but one (Aschengrau et al., 1993) of the case–control studies of bladder cancer reviewed by the committee used occupational history to assess exposure, and in some studies information on specific chemical exposures was also obtained (Gérin et al., 1998; Pesch et al., 2000a). The study by Aschengrau and colleagues assessed exposure on the basis of estimated doses of tetrachloroethylene found in public drinking water in five towns of Cape Cod, Massachusetts. Two studies included interviews with proxies if subjects were too ill to be interviewed (Morrison et al., 1985; Teschke et al., 1997). Most studies simply grouped exposure defined broadly on the basis of occupation, including work in the painting industry (Cordier et al., 1993; Jensen et al., 1987; La Vecchia et al., 1990; Morrison et al., 1985; Vineis and Magnani, 1985), in laundry and dry-cleaning services (Silverman et al., 1989a,b; Smith et al., 1985), and in both fields (Schoenberg et al., 1984; Teschke et al.,

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1997). Very low response rates were found in the study by Risch and colleagues (1988) of exposure to paints. A number of case–control studies used self-reported information on exposures that were not otherwise validated (Jensen et al., 1987; La Vecchia et al., 1990; Risch et al., 1988; Schoenberg et al., 1984; Smith et al., 1985; Vineis and Magnani, 1985) and thus may be subject to recall bias if the controls were not ill.

The main accepted risk factor for bladder cancer is cigarette smoking, and all but one (Smith et al., 1985) of the case–control studies of bladder cancer and exposure to specific and unspecified organic solvents reviewed by the committee accounted for smoking in some way. In most studies, subjects were asked whether they currently smoked; others inquired about the number of cigarettes smoked per day (Aschengrau et al., 1993), lifetime cigarette consumption (Risch et al., 1988), or duration of cigarette smoking (Schoenberg et al., 1984).

Case–control studies of bladder cancer and exposure to organic solvents that had reasonably good assessments of exposure, adequate control for confounding, and histologic confirmation of outcome include those by: Aschengrau et al., 1993; Cordier et al., 1993; Gérin et al., 1998; Pesch et al., 2000a; and Silverman et al., 1989a,b (see Table 6.27).

In addition to the case–control study by Pesch and colleagues (2000a) described above, there were several cohort studies of biologically monitored workers, transformer manufacturers, and aircraft and aerospace workers. One study of US aircraft-maintenance workers showed an $RR_{\text{any exposure}}$ of 1.2 (95% CI = 0.5–2.9) for bladder cancer (Blair et al., 1998); another showed no association (RR = 0.55, 95% CI = 0.18–1.28) (Boice et al., 1999). An increased risk of bladder cancer also was observed in a cohort of US aerospace-manufacturing workers (SMR = 1.36, 95% CI = 0.59–2.68) (Morgan et al., 1998). Three other cohort studies of workers biologically monitored for exposure to trichloroethylene, as shown by the presence of a urinary metabolite, showed no association (relative risks ranged from 0.61 to 1.1) between this marker and bladder cancer (Anttila et al., 1995; Axelson et al., 1994; Hansen et al., 2001). A nested case–control study within a cohort of transformer-assembly facility workers did not find an association between risk of bladder cancer and exposure to trichloroethylene (OR = 0.85, 95% CI = 0.32–3.32) (Greenland et al., 1994).

The case–control study by Pesch and colleagues (2000a) suggested a positive association with urothelial carcinoma (a cancer of the urinary tract that affects mostly the bladder). Using a job–exposure matrix, the authors found a 10% excess risk (OR = 1.1; 95% CI = 0.9–1.4) among men with "high" exposure and a 60% excess risk among women with "high" exposure (OR=1.6, 95% CI = 1.0–2.5). On the basis of the job task–exposure matrix, the magnitude of the OR for men with "high" exposure was increased to 1.3 (95% CI = 0.9–1.7). The job task–exposure matrix was not used to evaluate exposure of women.

The committee used two cohort studies and several case–control studies of dry-cleaning workers and other workers exposed to tetrachloroethylene in determining whether there is an association between exposure and bladder cancer. The two dry-cleaner cohort studies showed increased mortality from bladder cancer: Blair and colleagues (1990) reported an increased SMR of 1.7 (95% CI = 0.7–3.3), and Ruder and colleagues (2001) found a 122% increase in mortality from bladder cancer (SMR = 2.22, 95% CI = 1.06–4.08). The magnitude of the association was higher (SMR = 4.31, 95% CI = 1.85–8.76) among workers employed more than 5 years and in whom 20 years had passed since the first exposure.

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TABLE 6.27 Description of Case–Control Studies of Bladder Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Schoenberg et al., 1984	Male cases, age 21–84 years, with histologically confirmed diagnosis in New Jersey in February 1978–1979; controls identified through RDD (age 21–64 years) and HCFA records (age 65–85 years), stratified for age Response rates: 89.7% of cases, 86.6% of controls	658	1258	Painting or artistic work Dry-cleaning work	In-person interviews with questionnaires assessing lifetime occupational history (job titles)	Logistic regression	Age, duration of cigarette smoking, other occupations
Morrison et al., 1985	Cases, age 21–89 years, identified at hospitals in Boston; Greater Manchester County, UK; and Nagoya, Japan, in 1976–1978; controls selected from respective areas' electoral registers, matched for age and sex No response rates provided	430 Boston 399 UK 226 Japan	397 Boston 493 UK 443 Japan	Painting work	In-person interview (direct or proxy) assessing occupational history (job titles); job titles were coded	Logistic regression	Age, cigarette smoking
Smith et al., 1985	Cases and controls, age 21–84 years, residing in the nine SEER population-based areas and New Jersey, who participated in the NCI National Bladder Cancer Study; cases with histologically confirmed cancer; controls frequency matched for age and sex No response rates provided	7748 total participants with and without bladder cancer, classified as: worked in dry-cleaning operations ($N = 103$), experienced related exposures ($N = 5776$), or neither (unexposed; $N = 1869$)		Laundry and dry-cleaning work	In-person interview with structured questionnaire regarding occupational history (job or industry titles)	Logistic regression	Age, sex
Vineis and Magnani, 1985	Cases, age less than 70 years, identified from the Main Hospital in Torino, Italy, in 1978–1983; controls from same hospital diagnosed with benign urologic conditions, matched for age No response rates provided	512	596	Painting work	In-person interviews regarding lifetime occupational history (job or industry titles) obtained in hospital and blindly coded	Mantel-Haenszel	Age, smoking

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Jensen et al., 1987	Cases reported to the Danish Cancer Registry from Copenhagen area in 1979–1981, with 99% histologic verification; controls selected from the residents of the municipalities from which cases arose, matched for sex and age Response rates: 94.4% of cases, 75.1% of controls	371	771	Painting work	In-person interviews with questionnaire assessing occupational history (job titles and self-reported exposures)	Logistic regression	Age, sex, smoking
Risch et al., 1988	Cases, age 35–79 years, identified through a combination of cancer registry reporting and hospital record review in four cities in Canada in 1979–1982 with histologic confirmation; controls selected randomly from population listings and matched on birth year, sex, and residence area Response rates: 67% of cases, 53% of controls	826	792	Organic solvents Paints	In-person interview with questionnaire assessing specific occupational exposures (self-reports)	Conditional logistic regression	Matching variables, lifetime cigarette consumption
Silverman et al., 1989a	White cases, age 21–84 years, in 10 US areas in 1977–1978 with histologic confirmation; controls identified through RDD (age 21–64 years) and HCFA records (age 65–84 years), matched for age and geographic area No response rates provided	2100	3874	Dry-cleaning, ironing, and pressing work	Questionnaire administered by in-person interview (job or industry titles); industries and job titles coded by study authors and grouped by potential exposures	Logistic regression	Smoking, age
Silverman et al., 1989b	Nonwhite cases, same study as above (Silverman et al., 1989a)	126	383	See above	See above	See above	See above
La Vecchia et al., 1990	Cases, age less than 75 years, admitted to NCI or clinics and hospitals in Milan, Italy, in 1985–1988 with histologic confirmation; controls admitted to the same network of hospitals for acute nonneoplastic conditions Response rate: >97% of cases and controls	263	287	Painting work Chemical-industry work	Structured questionnaire to assess lifetime employment in 19 industries or occupations and 14 specific agents (job or industry titles and self-reported exposures)	Mantel-Haenszel	Age, sex, smoking

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Aschengrau et al., 1993	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from HCFA records and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 80.6% of cases, 75.9% of HCFA controls, 73.9% of RDD controls, 78.8% of next of kin of deceased controls	61	852	Tetrachloride-ethylene	Exposure dose estimated in areas of contaminated drinking water, accounting for location and years of residence, water flow, pipe characteristics	Logistic regression	Sex, age at diagnosis, vital status, educational level, usual number of cigarettes smoked, occupational exposure to solvents, specific cancer risk factors controlled for in respective analyses
Cordier et al., 1993	Cases, under age 80 years, from seven French hospitals in 1984–1987, with histologic confirmation; controls selected from the same hospitals from patients admitted for causes other than cancer, respiratory disease, or symptoms related to bladder cancer, matched for sex, age, ethnicity, and residence No response rates provided	765	765	Solvents Painting work	In-person interviews with segments on work histories (job titles); analyzed and coded by a team of experts in industrial hygiene	Logistic regression	Smoking status, hospital, age, place of residence
Teschke et al., 1997	Cases, age 19 years and over, registered with the British Columbia Cancer Agency in 1990–1991 with histologic confirmation; controls selected from the provincial voters list and matched on age and sex Response rates: 88.2% of cases, 80.3% of controls	105	139	Laundry personnel Painters	Occupational histories (job titles) and self-reported exposures obtained (direct or proxy) through standardized questionnaire (in-person or telephone interview)	Adjusted ORs	Sex, age, cigarette smoking

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Gérin et al., 1998	Male cases, age 35–75 years, diagnosed in one of 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls were also chosen from electoral lists and random-digit dialing Response rates: 82% of all cases, 71% of population controls	484	1066, consisting of 533 population controls and 533 randomly selected subjects from other cases of cancer	Benzene Toluene Xylene	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures on semiquantitative scales)	Logistic regression	Age, family income, ethnicity, cigarette smoking, respondent status
Pesch et al., 2000a	Cases from large hospitals in five regions in Germany in 1991–1995 with histologic confirmation; controls randomly selected from local residency registries matched on region, sex, and age Response rates: 84% of cases, 71% of controls	1035 urothelial	4298	Trichloro-ethylene Ethylene-ethylene Benzene Organic solvents	In-person interviews of lifetime occupational history using questionnaire to assess job titles and self-reported exposures; exposures ascertained by job–exposure matrixes	Logistic regression	Age, study center, smoking

NOTE: HCFA = Health Care Financing Administration; NCI = National Cancer Institute; SEER = Surveillance, Epidemiology, and End Results; RDD = random-digit dialing.

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Several case–control studies reported increased relative risks of bladder cancer with exposure in the dry-cleaning industry. Schoenberg and colleagues (1984) showed an OR of 1.33 (95% CI = 0.50–3.58), and Teschke and colleagues (1997) found an OR of 2.3 (95% CI = 0.4–13.9) in people ever employed as laundry personnel. Smith and co-workers (1985) showed an increased risk of bladder cancer among laundry and dry-cleaning workers, and this risk was higher among exposed smokers (OR = 3.94, 95% CI = 2.39–6.51) than among exposed nonsmokers (OR = 1.31, 95% CI = 0.85–2.03).

On the basis of exposure to tetrachloroethylene in public drinking water, Aschengrau and colleagues (1993) showed an OR of 1.16 (95% CI = 0.48–2.48) for low levels of exposure and an OR of 6.04 (95% CI = 1.32–21.84) for high levels of exposure. Using a job–exposure matrix, Pesch and colleagues (2000a) demonstrated an increased risk in men exposed to high levels of tetrachloroethylene (OR = 1.2, 95% CI = 1.0–1.5) and no increased risk in women (OR = 1.0, 95% CI = 0.6–1.9).

Two studies provided data on exposure to benzene and bladder cancer. Exposure to benzene, as assigned by industrial hygienists after reviewing detailed job histories, was not associated with bladder cancer in the Montreal case–control study (Gérin et al., 1998). In the study by Pesch and colleagues (2000a), there was an indication among men of risks increasing with increasing exposure on the basis of three methods of assessing exposure. For example, for "substantial" exposure to benzene, according to a British job–exposure matrix (Pannett et al., 1985), the RR of bladder cancer in men was 1.5 (95% CI = 1.0–2.1) and in women 1.4 (95% CI = 0.6–3.3) (Pesch et al., 2000a). However, the risks did not increase with increasing exposure among women according to the other two exposure-determination methods.

Three small occupational cohort studies (Svensson et al., 1990; Walker et al., 1993; Wiebelt and Becker, 1999) and a population-based case–control study (Gérin et al., 1998) found no evidence of an association between bladder cancer and exposure to toluene or xylene. Most of the estimates of RR were below unity, and the highest was 1.20 (95% CI = 0.25–3.51) in women working as shoe manufacturers (Walker et al., 1993).

The study that had the largest number of exposed cases was the cohort study of US painters and other union members that showed an increased risk of bladder cancer among painters (SMR = 1.23, 95% CI = 1.05–1.43) but not in nonpainters (SMR = 0.74, 95% CI = 0.46–1.11) (Steenland and Palu, 1999). A formal Poisson regression analysis comparing painters and nonpainters showed an RR of 1.77 (95% CI = 1.13–2.77) in painters. A smaller study of US painters (Matanoski et al., 1986) and a small study of paint-manufacturing workers (Morgan et al., 1981) showed no increased risk of bladder cancer (RR = 1.06, 95% CI = 0.78–1.41 and RR = 0.98 [no CI was available, and the committee was not able to calculate it], respectively). Boice and colleagues (1999) did not find an association in aircraft-manufacturing workers (SMR = 0.85, 95% CI = 0.49–1.35). Anttila and colleagues (1995) also found no increased risk of bladder cancer (SIR = 0.73, 95% CI = 0.24–1.71) among Finnish workers occupationally exposed to halogenated hydrocarbons. A cohort study of US aircraft-manufacturing workers in California showed a 26% excess risk of bladder cancer (SMR = 1.26, 95% CI = 0.74–2.03) (Garabrant et al., 1988). The study of US transformer-assembly workers showed a 21% increase in mortality (OR = 1.21, 95% CI = 0.49–2.98) (Greenland et al., 1994).

Pesch and colleagues (2000a) found an increased risk in painters in Germany who had a "very long" duration of exposure (OR = 1.6, 95% CI = 0.5–4.7) and in men who had "substantial" exposure to paints (OR = 1.6, 95% CI = 1.1–2.3). The authors did not show that the risk in painters increased with increasing duration of exposure (medium: OR = 1.3, 95% CI =

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0.6–2.6; long: OR = 0.7, 95% CI = 0.3–1.6l; very long: OR = 1.6, 95% CI = 0.5–4.7). Those analyses were adjusted for smoking. In British Columbia (Teschke et al., 1997), the risk was increased in people who had ever been employed as painters (OR = 2.8, 95% CI = 0.4–21.3) and after 20 years since first employment (OR = 2.0, 95% CI 0.1–33.0). The risk of bladder cancer increased in the Copenhagen study (OR = 2.54, 95% CI = 1.12–5.73) and increased with increasing duration of employment (1–19 years: OR = 1.6, 95% CI = 0.5–5.5; 20 years or more: OR = 4.1, 95% CI = 1.2–13.9) (Jensen et al., 1987). Positive associations were also found in studies in Milan (OR = 1.8, 95% CI = 0.8–3.7) (La Vecchia et al., 1990), Canada (OR = 1.18, 95% CI = 0.87–1.62) (Risch et al., 1988), Boston (OR = 1.5, 95% CI 0.9–2.4) (Morrison et al., 1985), and New Jersey (OR = 1.53, 95% CI = 0.96–2.44) (Schoenberg et al., 1984).

Summary and Conclusions

Several studies of trichloroethylene and bladder cancer showed weak and imprecise associations. Most suffered from low statistical power and probable exposure misclassification, so the committee concluded that there was insufficient evidence to determine whether an association exists.

For exposure to tetrachloroethylene and dry-cleaning solvents, a number of cohort and case–control studies showed a positive association between exposure and risk of bladder cancer. Therefore, the committee judged that the data, though limited, was suggestive of an association.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to tetrachloroethylene and dry-cleaning solvents and bladder cancer.

Based on the consistency of association in the case–control studies (Jensen et al., 1987; Morrison et al., 1985; Pesch et al., 2000b; Schoenberg et al., 1984) and the positive findings in the US cohorts of painters (Steenland and Palu, 1999) and aircraft workers (Garabrant et al., 1988), the committee decided that the evidence between exposure to unspecified mixtures of organic solvents and bladder cancer was both limited and suggestive of an association.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and bladder cancer.

In contrast, the committee considered the findings for exposure to benzene and risk of bladder cancer to be inconsistent. The studies on toluene and xylene did not find an association. Table 6.28 identifies the studies used by the committee in making its conclusions, and unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to other solvents under review and bladder cancer.

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TABLE 6.28 Selected Epidemiologic Studies—Bladder Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males, ever exposed	10	1.1 (0.5–2.0)
	Females, ever exposed	0	—
Blair et al., 1998	Aircraft maintenance in Utah		
	No trichloroethylene exposure	10	1.3 (0.5–3.5)
	<5 unit-years	13	1.7 (0.6–4.4)
	5–25 unit-years	9	1.7 (0.6–4.9)
Anttila et al., 1995	Finnish workers occupationally exposed		
	Entire period since first measurement	5	0.82 (0.27–1.90)
	0–9	1	0.65 (0.02–3.59)
	10–19	2	0.61 (0.07–2.22)
	20+	2	1.51 (0.18–5.44)
Axelson et al., 1994	Swedish men, occupationally exposed	8	1.02 (0.44–2.00)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, routine exposure	5	0.55 (0.18–1.28)
Blair et al., 1998	Aircraft maintenance workers in Utah		
	Any exposure	17	1.2 (0.5–2.9)
	No trichloroethylene exposure	4	0.7 (0.2–2.8)
	<5 unit-years	7	1.8 (0.5–6.2)
	5–25 unit-years	5	2.1 (0.6–8.0)
	Low-level intermittent	10	1.5 (0.4–4.8)
	Low-level continuous	9	2.0 (0.6–6.4)
Morgan et al., 1998	Aerospace workers in Arizona		
	Any exposure	8	1.36 (0.59–2.68)
	Low exposure	1	0.51 (0.01–2.83)
	High exposure	7	1.79 (0.72–3.69)
Greenland et al., 1994	White male US transformer manufacturers, ever exposed	NA	0.85 (0.32–3.32)
Case–Control Study			
Pesch et al., 2000a	Participants in multiple centers in Germany		
	German job–exposure matrix		
	Trichloroethylene (males)		
	Medium	154	1.1 (0.8–1.3)
	High	182	1.1 (0.9–1.4)
	Substantial	68	1.3 (0.9–1.7)
	Trichloroethylene (females)		
	Medium	21	1.0 (0.6–1.7)
	High	32	1.6 (1.0–2.5)
	Substantial	3	0.6 (0.2–2.3)
	Job task–exposure matrix approach		
	Trichloroethylene (males)		
	Medium	47	0.8 (0.6–1.2)
	High	74	1.3 (0.9–1.7)
	Substantial	36	1.8 (1.2–2.7)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Studies—Mortality			
Ruder et al., 2001	Dry-cleaning labor-union workers	10	2.22 (1.06–4.08)
	≥5 years exposure with >20 years latency	8	4.31 (1.85–8.76)
	Tetrachloroethylene plus other solvents (likely Stoddard)	10	3.15 (1.51–5.79)
Blair et al., 1990	Members of a dry-cleaning union in St. Louis, MO	8	1.7 (0.7–3.3)
Case–Control Studies			
Pesch et al., 2000a	Participants in multiple centers in Germany		
	German job–exposure matrix		
	Tetrachloroethylene (males)		
	Medium	162	1.1 (0.9–1.3)
	High	172	1.2 (1.0–1.5)
	Substantial	71	1.4 (1.0–1.9)
	Tetrachloroethylene (females)		
	Medium	21	1.8 (1.0–3.0)
	High	16	1.0 (0.6–1.9)
	Substantial	3	0.7 (0.2–2.5)
	Job task–exposure matrix approach		
	Tetrachloroethylene (males)		
	Medium	37	1.0 (0.7–1.5)
	High	47	1.2 (0.8–1.7)
	Substantial	22	1.8 (1.1–3.1)
Teschke et al., 1997	Residents of British Columbia, Canada		
	Laundry personnel, ever employed	5	2.3 (0.4–13.9)
	Laundry personnel, most recent 20 years removed	4	1.8 (0.3–11.3)
Aschengrau et al., 1993	Residents of upper Cape Cod, MA		
	Any exposure (no latency)	13	1.55 (0.74–3.01)
	Low exposure	9	1.16 (0.48–2.48)
	High exposure	4	6.04 (1.32–21.84)
Silverman et al., 1989b	Nonwhite males in 10 US areas		
	Dry cleaner, ironer, or presser, ever employed	11	2.8 (1.1–7.4)
	<5 years duration	7	5.3
	5+ years duration	4	1.8
Smith et al., 1985	Incident cases in 10 US areas		
	Laundry and dry cleaners, ever employed		
	Nonsmoker	NA	1.31 (0.85–2.03)
	Former smoker	NA	2.99 (1.80–4.97)
	Current smoker	NA	3.94 (2.39–6.51)
	Chemically related exposure group		
	Nonsmoker	NA	1.11 (0.99–1.25)
	Former smoker	NA	2.01 (1.69–2.40)
	Current smoker	NA	3.12 (2.62–3.71)
Schoenberg et al., 1984	Male residents of New Jersey		
	Dry-cleaning, ever employed	7	1.33 (0.50–3.58)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Case–Control Studies			
Pesch et al., 2000a	Participants in multiple centers in Germany		
	British job–exposure matrix		
	Benzene (males)		
	Medium	95	1.1 (0.8–1.4)
	High	70	0.9 (0.7–1.2)
	Substantial	47	1.5 (1.0–2.1)
	Benzene (females)		
	Medium	21	1.2 (0.7–2.0)
	High	18	1.5 (0.9–2.8)
	Substantial	8	1.4 (0.6–3.3)
	German job–exposure matrix		
	Benzene (males)		
	Medium	177	1.1 (0.9–1.3)
	High	169	1.2 (1.0–1.6)
	Substantial	68	1.2 (0.8–1.6)
	Benzene (females)		
	Medium	27	1.0 (0.7–1.7)
	High	23	0.8 (0.5–1.4)
	Substantial	5	0.6 (0.2–1.6)
	Job task–exposure matrix approach		
	Benzene (males)		
	Medium	51	0.7 (0.5–1.0)
	High	71	1.0 (0.7–1.3)
	Substantial	37	1.4 (0.9–2.1)
	Benzene (females)		
	Medium	2	0.4 (0.1–1.8)
	High	3	0.4 (0.1–1.2)
	Substantial	2	0.8 (0.2–3.7)
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	65	1.0 (0.7–1.3)
	Medium exposure	22	1.2 (0.7–2.0)
	High exposure	2	0.2 (0.0–0.6)
Toluene			
Cohort Study—Incidence			
Svensson et al., 1990	Male rotogravure printers in Sweden, employed >3 months		
	Bladder and kidney cancer	4	0.64 (0.18–1.65)
	≥5 yrs exposed with >10 yrs latency	4	0.85 (0.23–2.16)
Cohort Study—Mortality			
Wiebelt and Becker, 1999	Male German rotogravure printers, employed >1 year	2	0.66 (0.08–3.27)
Walker et al., 1993	Shoe manufacturers in two plants in Ohio, potentially exposed to toluene and other solvents		
	Total	7	0.99 (0.40–2.05)
	Males	4	0.87 (0.24–2.25)
	Females	3	1.20 (0.25–3.51)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Svensson et al., 1990	Male rotogravure printers in Sweden, employed >3 months		
	Bladder and kidney cancer	1	0.45 (0.01–2.53)
	≥5 yrs exposed with >10 yrs latency	1	0.57 (0.01–3.20)
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	52	0.9 (0.6–1.3)
	Medium exposure	6	0.3 (0.1–0.7)
	High exposure	7	1.0 (0.4–2.5)
Xylene			
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	35	0.8 (0.5–1.1)
	Medium exposure	16	1.0 (0.5–1.8)
	High exposure	3	0.8 (0.2–3.2)
Unspecified Mixtures of Organic Solvents			
Cohort Study–Incidence			
Anttila et al., 1995	Finnish workers monitored for exposure		
	Halogenated hydrocarbons	5	0.73 (0.24–1.71)
Cohort Studies–Mortality			
Steenland and Palu, 1999	US painters and other union members		
	Painters	166	1.23 (1.05–1.43)
	20 years since membership	146	1.25 (1.06–1.47)
	Nonpainters	22	0.74 (0.46–1.11)
	20 years since membership	19	0.84 (0.51–1.31)
	Poisson regression comparing painters with nonpainters:		
	Rate ratio	166	1.77 (1.13–2.77)
	Rate ratio, ≥20 years since membership	146	1.55 (0.96–2.51)
Greenland et al., 1994	White male US transformer-assembly workers	NA	1.21 (0.49–2.98)
	Solvents, ever exposed		
Garabrant et al., 1988	Aircraft-manufacturing workers in California		
	Entire cohort	17	1.26 (0.74–2.03)
	25–29 years of employment	2	2.66 (0.32–9.50)[a]
	30+ years of employment	1	2.45 (0.06–13.59)[a]
Matanoski et al., 1986	US painters and allied tradesmen union members	48	1.06 (0.78–1.41)
Morgan et al., 1981	Male US paint and coatings manufacturers, employed >1 year	16	0.98
Walker et al., 1993	Shoe-manufacturing workers in Ohio, potentially exposed	7	0.99 (0.40–2.05)
	Males	4	0.87 (0.24–2.25)
	Females	3	1.20 (0.25–3.51)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Studies			
Pesch et al., 2000a	Residents of multiple centers in Germany		
	Duration of exposure—painters:		
	Medium	12	1.3 (0.6–2.6)
	Long	6	0.7 (0.3–1.6)
	Very long	5	1.6 (0.5–4.7)
	Job–exposure approach, organic solvents:		
	Males, substantial exposure	43	1.4 (0.9–2.0)
	Females, substantial exposure	8	1.5 (0.6–3.5)
	Job–exposure approach, paints:		
	Males, substantial exposure	38	1.6 (1.1–2.3)
	Females, substantial exposure	2	0.3 (0.1–1.13)
	Job task–exposure matrix, paints:		
	Males, substantial exposure	33	1.5 (1.0–2.3)
	Females, substantial exposure	10	2.1 (1.0–4.4)
Teschke et al., 1997	Painters in British Columbia, Canada		
	Ever employed	4	2.8 (0.4–21.3)
	20 years since employment	2	2.0 (0.1–33.0)
Cordier et al., 1993	Residents of France		
	Painter, ever employed	19	0.97 (0.50–1.88)
	Solvents, ever exposed	171	1.28 (0.98–1.68)
La Vecchia et al., 1990	Residents of Milan, Italy		
	Painting, ever employed	NA	1.8 (0.8–3.7)
	Chemical industry, ever exposed	NA	1.7 (0.9–3.3)
Silverman et al., 1989a	White males employed as painters		
	<5 years	50	1.7
	5–9 years	14	0.9
	10–24 years	26	1.6
	25+ years	22	1.9
Risch et al., 1988	Residents of Canada		
	Organic solvents, ever exposed	208	1.14 (0.82–1.57)
	Organic solvents, exposed 8–28 years	NA	1.03 (0.70–1.52)
	Paints, ever exposed	204	1.18 (0.87–1.62)
	Paints, exposed 8–28 years	NA	1.11 (0.77–1.60)
Jensen et al., 1987	Residents of Copenhagen, Denmark		
	Painting, ever employed	13	2.54 (1.12–5.73)
	1–19 years	5	1.6 (0.5–5.5)
	≥20 years	8	4.1 (1.2–13.9)
Vineis and Magnani, 1985	Painters in Turin, Italy		
	Painter in building industry	12	1.0 (0.4–2.2)
	Painter in carpentry	1	0.6 (0.04–8.4)
	Car painter	7	2.0 (0.6–7.0)
	Spray-painter	2	1.2 (0.2–5.8)
Morrison et al., 1985	Residents occupationally exposed to paints		
	Boston, MA	35	1.5 (0.9–2.4)[b]
	Manchester, UK	23	0.7 (0.5–1.2)[b]
	Nagoya, Japan	5	0.7 (0.3–1.7)[b]

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Schoenberg et al., 1984	Male painters or artists in New Jersey, ever employed	39	1.53 (0.96–2.44)

NOTE: NA = not available.
[a]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.
[b]90% CI.

Epidemiologic Studies of Exposure to Organic Solvents and Kidney Cancer

Exposure to organic solvents was determined by using responses from in-person interviews or structured questionnaires about job titles and occupational and industrial exposures. Many of the studies reviewed on kidney cancer included small numbers of cases, which limited their statistical power. Several of the studies with large numbers of cases used self-reports to determine exposure, including those by: Asal et al., 1988; Dosemeci et al., 1999; Jensen et al., 1988; Mandel et al., 1995; McCredie and Stewart, 1993; Mellemgaard et al., 1994; Schlehofer et al., 1995; Sharpe et al., 1989; and Vamvakas et al., 1998. Such exposure determinations may be subject to misclassification errors that would affect risk estimates.

Although several studies included assessment of risk associated with specific solvent exposure, exposure was based on job titles that were then linked to potential exposure information determined by a job–exposure matrix or by industrial hygienists (Harrington et al., 1989; Partanen et al., 1991; Pesch et al., 2000b). Risk factors for kidney cancer that would require consideration in analyses are not well established.

Like the studies of bladder cancer, the case–control studies considered by the committee to be of relatively high quality had good information on exposure, controlled adequately for confounding, and used histologic confirmation of outcomes (Aschengrau et al., 1993; Asal et al., 1988; Gérin et al., 1998; Partanen et al., 1991; and Pesch et al., 2000b) (see Table 6.29).

Kidney cancer was not associated with exposure to trichloroethylene in three studies of biologically monitored workers in Scandinavian countries (Anttila et al., 1995; Axelson et al., 1994; Hansen et al., 2001) or in a study of US transformer manufacturers (Greenland et al., 1994). In the study by Anttila and colleagues, the SIR was 0.87 (95% CI = 0.32–1.89) in all workers exposed, 1.16 (95% CI = 0.42–2.52) in Swedish men in Axelson and colleagues' study, and 0.9 (95% CI = 0.2–2.6) in Danish workers in Hansen and colleagues' study. Greenland and colleagues showed an OR of 0.99 (95% CI = 0.30–3.32) in the transformer cohort. Three cohort studies of workers in aircraft and aerospace industries were inconsistent; no association (SMR = 0.99, 95% CI = 0.40–2.04) was found in a California aircraft-manufacturing study (Boice et al., 1999). Studies of aircraft-maintenance workers in Utah (Blair et al., 1998) and aerospace workers in Arizona (Morgan et al., 1998) showed increased relative risks but no exposure–response relationships.

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TABLE 6.29 Description of Case–Control Studies of Kidney Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Asal et al., 1988	Cases from 29 hospitals in Oklahoma diagnosed and confirmed in 1981–1984; hospital controls selected from the same hospitals and matched on age, sex, race, hospital, and date of admission; population-based controls selected through RDD No response rates provided	315 renal cell carcinoma	313 hospital 336 population	Dry-cleaning work Painter or paint-manufacturing work	In-person interview assessing occupations (job titles) and industrial exposures	Logistic regression	Weight, age, alcohol consumption, occupations, smoking, snuff use, coffee consumption, kidney stones, hypertension, other medical factors
Jensen et al., 1988	Cases, under age 80 years, reported to the Danish Cancer Registry from Copenhagen and the surrounding island of Sjaelland in 1979–1982, with 90% histologic verification; controls selected from the hospitals from which cases arose, excluding those with urinary tract and smoking-related diseases; controls matched for hospital, sex, and age Response rates: 99.0% of cases, 100.0% of controls	96 renal pelvis and ureter	288	Painter or paint-manufacturing work	In-person interviews with questionnaire assessing personal habits and occupational history (job or industry titles and self-reported exposures)	Logistic regression	Sex, lifetime tobacco smoking
Harrington et al., 1989	Cases diagnosed and histologically confirmed in 1984–1985 and reported to the West Midlands Regional Cancer Registry (UK); controls randomly selected from practitioner records and matched for age, sex, ethnicity, location, and socioeconomic group No response rates provided	54 renal	54	Solvents	In-person interviews with questionnaire assessing lifetime occupational history (job titles); exposure indexes determined by occupational hygienist or chemist	Matched analyses	None

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Sharpe et al., 1989	Cases diagnosed at one of four Montreal-area hospitals in 1982–1986 and one of five other hospitals in 1982–1987; cases were histologically confirmed and alive at time of chart review; controls selected from suspected renal-cell carcinoma cases, but final diagnoses were not cancer; matched 1:1 for sex, age, and urologist Response rate: 97% overall	164 renal	161	Organic solvents	History of exposure to hydrocarbons obtained through mailed questionnaire and supplemented by telephone interview (self-reports)	Univariate analysis	None
Partanen et al., 1991	Cases, age over 20 years, identified through the Finnish Cancer Registry in 1977–1978; controls randomly selected from the Population Register Centre matched for year of birth, sex, and survival status Response rates: 69% of cases, 68% of controls	408 renal cell	819	Nonchlorinated solvents	Mailed questionnaire or phone interview (direct or proxy) assessing lifetime occupational history (job or industry titles); industrial hygienist coded and assigned summary indicators of specific exposures	Conditional logistic regression	Matching variables, smoking, coffee consumption, obesity
Aschengrau et al., 1993	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from HCFA records and RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 80.6% of cases, 75.9% of HCFA controls, 73.9% of RDD controls, 78.8% of next of kin of deceased controls	35 kidney	777	Ethylene-ethylene	Exposure dose estimated in areas of contaminated drinking water, accounting for location and years of residence, water flow, pipe characteristics	Logistic regression	Sex, age at diagnosis, vital status, educational level, usual number of cigarettes smoked, occupational exposure to solvents, specific cancer risk factors controlled for in respective analyses

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
McCredie and Stewart, 1993	Cases, age 20–79 years, among residents of New South Wales in 1989–1990 identified from the New South Wales Central Cancer Registry and from physicians; controls selected from electoral rolls and matched on age distribution No response rates provided	489 renal cell 147 renal pelvic	523	Dry-cleaning industry work	Questionnaire (in-person interview or mailed with telephone followup) to assess employment in specific occupations and industries (job or industry titles)	Logistic regression	Age, sex, interview method, cigarette smoking, body mass index, education, analgesics use
Mellemgaard et al., 1994	Cases, age 20–79 years, identified from the Danish Cancer Registry and pathology departments in 1989–1992 with histologic confirmation; controls selected from the Central Population Register and matched for age and sex Response rates: 93.2% of cases, 85.6% of controls	368 renal cell	396	Dry-cleaning work Solvents	In-person interviews with questionnaire assessing most recent and longest-held occupation (job titles) and exposure to specific agents (self-reports)	Logistic regression	Age, body mass index, smoking
Mandel et al., 1995	Cases, age 20–79 years, from six international sites, diagnosed and confirmed in 1989–1991 using cancer registries or surveillance of clinical and pathology departments; controls selected from population registers, electoral rolls, residential lists, HCFA records, or RDD, depending on the site; controls matched on age and sex No response rates provided (Related to McCredie and Stewart, 1993)	1732 renal	2309	Dry-cleaning solvents Dry-cleaning work	In-person interviews to assess lifetime occupational history (job titles) and exposure to specific agents (self-reports)	Logistic regression	Age, center, body-mass index, cigarette smoking
Schlehofer et al., 1995	Cases, age 20–75 years, identified through 10 urology departments in the Rhein-Neckar-Odenwald area of Germany in 1989–1991 with histologic confirmation; controls randomly selected from population register and matched on age and sex Response rates: 97.3% of cases, 75% of controls	277 renal cell	286	Chlorinated solvents	In-person interview with questionnaire assessing exposure (in excess of 5 years) from list of specific substances (self-reports)	Logistic regression	

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Gérin et al., 1998	Male cases, age 35–75 years, diagnosed in one of 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls were also chosen from electoral lists and random-digit dialing Response rates: 82% of all cases, 71% of population controls	177 kidney	1066, consisting of 533 population controls and 533 randomly selected subjects from other cases of cancer	Benzene Toluene Xylene	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures on semiquantitative scales)	Logistic regression	Age, family income, ethnicity, cigarette smoking, respondent status
Vamvakas et al., 1998	Cases who underwent nephrectomy in 1987–1992 in a German hospital; controls selected from accident wards of three nearby hospitals Response rates: 85% of cases, 75% of controls	58 renal	84	Trichloroethylene	In-person interview (direct or proxy) with structured questionnaire assessing occupational history (job titles) and specific agent exposures (self-reports)	Logistic regression	Age, sex, smoking, body mass index, blood pressure, intake of diuretics
Dosemeci et al., 1999	White cases, age 20–85 years, with histologically confirmed diagnosis identified through the Minnesota Cancer Surveillance System in 1988–1990; controls identified through RDD (age 21–64 years) and HCFA records (age 65–85 years), stratified for age and sex Response rates: 87% of cases, 86% of controls	438 renal cell carcinoma	687	Trichloroethylene Tetrachloroethylene Solvents in general	In-person interviews (direct or proxy) with questionnaire assessing occupational history; job titles were coded and merged with a job–exposure matrix from NCI	Logistic regression	Age, smoking, hypertension, body mass index
Pesch et al., 2000b	Cases in large hospitals in five regions in Germany in 1991–1995 with histologic confirmation; controls randomly selected from local residency registries matched on region, sex, and age. Response rates: 88% of cases, 71% of controls	935 renal-cell	4298	Trichloroethylene Tetrachloroethylene Organic solvents	In-person interviews of lifetime occupational history using questionnaire to assess job titles and self-reported exposures; exposures ascertained by job–exposure matrixes	Conditional logistic regression	Matching variables, smoking

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing.

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A small cohort study of German cardboard manufacturers exposed to trichloroethylene showed an increased risk of kidney cancer (SIR = 7.97, 95% CI 2.59–8.59 and SMR = 3.28, 95% CI = 0.40–11.84) (Henschler et al., 1995). A case–control study using different cases from the same area as that investigated by Henschler and colleagues also showed an increased risk of kidney cancer (OR = 10.8, 95% CI = 3.36–34.75) (Vamvakas et al., 1998). A case–control study of kidney cancer in Minnesota showed an association only in women (OR = 1.96, 95% CI = 1.0–4.0) (Dosemeci et al., 1999). Pesch and colleagues (2000b) showed an increased risk of kidney cancer in men but not women with substantial exposure to trichloroethylene (OR = 1.3, 95% CI = 0.9–1.8; OR = 0.8, 95% CI = 0.3–1.9, respectively).

Some of the studies described above that investigated the risk of bladder cancer and exposure to tetrachloroethylene or dry-cleaning solvents also provided results on kidney cancer. The cohort studies of dry-cleaning workers had few exposed cases, and the associations had wide confidence intervals. Ruder and colleagues (2001) reported an increased risk of kidney cancer in dry-cleaning union workers (SMR = 1.41, 95% CI = 0.46–3.30) and in workers exposed to tetrachloroethylene only (SMR = 1.73, 95% CI = 0.21–6.25). The study by Blair and colleagues (1990) of dry-cleaning union members found no increased risk of kidney cancer (SMR = 0.5, 95% CI = 0.1–1.8), and Anttila and colleagues (1995) reported an increased risk of kidney cancer among workers occupationally exposed to tetrachloroethylene (SIR = 1.82, 95% CI = 0.22–6.56).

Pesch and colleagues (2000b) found an OR of 1.4 (95% CI = 1.0–2.0) in men who had "substantial" exposure to tetrachloroethylene according to the German job–exposure matrix; the OR in women was 0.7 (95% CI = 0.3–2.2). Mandel and colleagues (1995) also observed an increased risk of kidney cancer among those ever exposed to dry-cleaning solvents (OR = 1.4, 95% CI = 1.1–1.7). Both studies included large numbers of exposed cases, and the analyses were adjusted for smoking. Although a study of dry cleaners in Germany also reported an association with kidney cancer (OR = 2.52, 95% CI = 1.23–5.16), the authors indicated that subjects were exposed to a combination of tetrachloroethylene and tetrachlorocarbonate. The latter is a solvent not on the committee's list to review, so this study (Schlehofer et al., 1995) was not considered critical to the committee's review of tetrachloroethylene.

Other case–control studies reported associations with kidney cancer. Dosemeci and colleagues showed an OR of 1.12 (95% CI = 0.7–1.7) in men exposed to tetrachloroethylene in Minnesota but an OR of 0.82 (95% CI = 0.3–2.1) in women. A case–control study of dry cleaners in Denmark (Mellemgaard et al., 1994) showed an OR of 2.3 (95% CI = 0.2–2.7) in men and an OR of 2.9 (95% CI = 0.3–33) in women. A study in New South Wales (McCredie and Stewart, 1993) showed ORs of 2.49 (95% CI = 0.97–6.35) for renal cancer and 4.68 (95% CI = 1.32–16.56) for renal pelvic cancer. Another study of dry cleaners in Oklahoma (Asal et al., 1988) found an OR of 8.7 (95% CI = 0.9–81.3) for kidney cancer. A study of residents in Cape Cod, Massachusetts (Aschengrau et al., 1993), reported an OR of 1.23 (95% CI = 0.45–3.45) for kidney cancer after any exposure to tetrachloroethylene.

Gérin and colleagues (1998) investigated the risk of kidney cancer and exposure to benzene, toluene, and xylene; a weak association with no apparent exposure–response relationship was found for exposure to benzene (low exposure: OR = 1.2, 95% CI = 0.7–1.9; medium or high exposure: OR = 1.3, 95% CI = 0.7–2.4). No association was found for either toluene (medium or high exposure: OR = 1.0, 95% CI = 0.5–2.1) or xylene (medium or high exposure: OR = 1.0, 95% CI = 0.4–2.4).

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The committee reviewed two other studies that investigated the association between kidney cancer and exposure to toluene. Wiebelt and Becker (1999) found no association (OR = 0.49, 95% CI = 0.06–2.34), and Walker and colleagues (1993) reported an increased risk in men who were potentially exposed to toluene in the shoe-manufacturing industry (SMR = 1.71, 95% CI = 0.62–3.73).

A cohort study of US isopropyl manufacturers found an association (SMR = 6.45, 95% CI = 0.78–23.29) between exposure to isopropyl alcohol and kidney cancer (Alderson and Rattan, 1980).

The committee reviewed several cohort studies of painters and workers in aircraft manufacturing (Boice et al., 1999; Garabrant et al., 1988), shoe manufacturing (Fu et al., 1996; Walker et al., 1993), transformer assembly (Greenland et al., 1994), and petroleum refining (Poole et al., 1993) and several case–control studies conducted in Minnesota (Dosemeci et al., 1999), Denmark (Mellemgaard et al., 1994), New South Wales (McCredie and Stewart, 1993), Finland (Partanen et al., 1991), and the United Kingdom (Harrington et al., 1989).

The largest cohort study of painters showed no association between being a painter and kidney cancer (SMR = 1.06, 95% CI = 0.86–1.29) (Steenland and Palu, 1999), but a positive association was found in other cohorts of painters, including a study by Matanoski and colleagues (1986) (SMR = 1.28, 95% CI = 0.91–1.76). A study of paint-manufacturing workers showed no association with kidney cancer (SMR = 0.39) (Morgan et al., 1981). Several case–control studies that considered occupation as a painter or in paint manufacturing reported positive associations with kidney cancer (Asal et al., 1988: OR = 1.3, 95% CI = 0.7–2.6; Jensen et al., 1988: OR = 1.8, 95% CI = 0.7–4.6). Pesch and colleagues (2000b) found that relative risks increased with increasing duration of exposure (medium: OR = 1.6, 95% CI = 0.8–3.0; very long: OR = 2.3, 95% CI 0.8–6.8).

No evidence of an association between exposure to unspecified mixtures of solvents and kidney cancer was found in two cohorts of aircraft manufacturers in California (Boice et al., 1999: SMR = 0.81, 95% CI = 0.44–1.36; Garabrant et al., 1988: SMR = 0.93, 95% CI = 0.48–1.64), and the association decreased with increasing years of exposure (Boice et al., 1999). No association was found in an incidence study of Finnish workers monitored for halogenated hydrocarbon exposure (SIR = 0.89, 95% CI = 0.36–1.82) (Anttila et al., 1995) or among US petroleum-refinery workers exposed to aromatic hydrocarbons (OR = 0.95, 95% CI = 0.50–1.80). However, a study of dry cleaners in Germany exposed to a mixture of solvents, including tetrachloroethylene and tetrachlorocarbonate, reported an association with kidney cancer (OR = 2.52, 95% CI = 1.23–5.16) (Schlehofer et al., 1995), as did a study of US transformer-assembly workers exposed to solvents (OR = 1.64, 95% CI = 0.49–5.50) (Greenland et al., 1994). Two cohort studies of shoe-manufacturing workers also showed an increased association, including Fu and colleagues' (1996) study of Florence workers (SMR = 4.00, 95% CI = 0.83–11.69 for high solvent exposure) and Walker and colleagues' (1993) study (SMR = 1.71, 95% CI = 0.62–3.73 among men; the SMR was 0.97 among women).

Case–control studies that analyzed self-reported exposure to organic solvents include studies conducted in Minnesota (Dosemeci et al., 1999) and Denmark (Mellemgaard et al., 1994). The study in Minnesota showed ORs close to 1.0: in men, it was 1.12 (95% CI = 0.7–1.7), and in women it was 0.82 (95% CI = 0.3–2.1). The study in Denmark showed increased risks in both men (OR = 2.3, 95% CI = 0.2–27) and women (OR = 2.9, 95% CI = 0.3–33). Other case–control studies reported an association between kidney cancer and nonchlorinated solvents (Partanen et al., 1991: OR = 3.46, 95% CI = 0.91–13.2) and organic solvents (Sharpe et al.,

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1989: OR = 1.68, 95% CI = 0.89–3.18). Pesch and colleagues (2000b) found positive associations between exposure to organic solvents specifically, using a job–exposure matrix, and to solvents broadly, using a job task–exposure matrix. The relative risks in men were increased on the basis of the job–exposure matrix (OR = 1.6, 95% CI = 1.1–2.3) and the job task–exposure matrix (OR = 1.5, 95% CI = 1.0–2.3). The risks were increased in women on the basis of the job task–exposure matrix (OR = 2.1, 95% CI = 1.0–4.4), but not the job–exposure matrix (OR = 0.3, 95% CI = 0.1–1.3). No association was found in the study by Harrington and colleagues (1989) that examined exposure to solvents in the UK (OR = 1.0, 95% CI = 0.2–4.9).

Summary and Conclusions

Because of their small numbers of cases, most studies on exposure to trichloroethylene and kidney cancer lacked the power to detect excess risks. Although positive associations were suggested by three studies (Henschler et al., 1995; Pesch et al., 2000b; Vamvakas et al., 1998), one was based on self-reported exposures (Vamvakas et al., 1998), and the committee was concerned about bias. The committee did not find the results of the other case–control study to be persuasive (Pesch et al., 2000b). The findings of the cohort study (Henschler et al., 1995) were based on a cluster of cases. For exposure to benzene, toluene, xylene, and isopropyl alcohol, there was only a small number of studies available, and they lacked consistently positive findings. Therefore, the committee determined that the evidence for these exposes was insufficient to determine whether an association exists for kidney cancer.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than tetrachloroethylene and dry-cleaning solvents, and kidney cancer.

For exposure to tetrachloroethylene and dry-cleaning solvents, positive associations were observed in several well-conducted studies (Mandel et al., 1995; McCredie and Stewart, 1993; Pesch et al., 2000b), and the committee determined that the evidence between exposure to tetrachloroethylene and dry-cleaning solvents and risk of kidney cancer was limited/suggestive of an association.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to tetrachloroethylene and dry-cleaning solvents and kidney cancer.

Although several case–control studies showed an increased risk of kidney cancer with exposure to unspecified mixtures of organic solvents (including Dosemeci et al., 1999; Jensen et al., 1988; Mellemgaard et al., 1994; Partanen et al., 1991; Pesch et al., 2000b; and Sharpe et al., 1989), several cohort studies did not, including the largest study of painters (Steenland and Palu, 1999), the painter study by Morgan and colleagues (1981), two studies of aircraft manufacturers (Boice et al., 1999; Garabrant et al., 1988), a biologically monitored study (Anttila et al., 1995), and a study on petroleum-refinery workers (Poole et al., 1993). As a result, the committee was unable to reach a consensus on an association between kidney cancer and exposure to organic solvents. Some committee members believed that the evidence was limited/suggestive, and others believed that it was inadequate/insufficient to determine whether an association exists. In evaluating each study and the overall body of evidence, committee members differed in their judgment about the extent to which bias and confounding affected the results.

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The large number of positive findings from the case–control studies, especially among women, and the use of a job–exposure matrix by Pesch and colleagues (2000b) were supportive of a conclusion that the evidence was limited/suggestive of an association between exposure to unspecified mixtures of solvents and kidney cancer. In contrast, the lack of positive findings in large cohorts of occupationally exposed populations—such as painters, aircraft manufacturers, and petroleum refinery workers—and in a biologically monitored cohort of Finnish workers (Anttila et al., 1995), the lack of increased risks as exposure and duration of exposure increased (Boice et al., 1999), and the large number of case–control studies that relied on self-reported exposures (Asal et al., 1988; Dosemeci et al., 1999; Jensen et al., 1988; McCredie and Stewart, 1993; Mellemgaard et al., 1994; Schlehofer et al., 1995; Sharpe et al., 1989) supported a conclusion that the evidence was inadequate/insufficient to determine whether an association exists.

Thus, the committee could not reach a consensus conclusion for kidney cancer and exposure to unspecified mixtures of organic solvents. As more studies are conducted on organic solvents and the risk of kidney cancer, future committees may revisit this literature in evaluating the evidence of association.

The studies reviewed by the committee in making its conclusions are identified below in Table 6.30. Unless indicated in the table, the study populations include both men and women.

TABLE 6.30 Selected Epidemiologic Studies—Kidney Cancer and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males, ever exposed	3	0.9 (0.2–2.6)
	Females, ever exposed	1	2.4 (0.03–14)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No exposure	9	1.6 (0.5–5.4)
	<5 unit-years	9	1.4 (0.4–4.7)
	5–25 unit-years	5	1.3 (0.3–4.7)
Henschler et al., 1995	Male German cardboard manufacturers, employed >1 year	5	7.97 (2.59–8.59)
Anttila et al., 1995	Finnish workers occupationally exposed		
	Entire period since first measurement	6	0.87 (0.32–1.89)
	0–9	1	0.53 (0.01–2.95)
	10–19	5	1.39 (0.45–3.24)
	20+	0	— (0.00–2.48)
Axelson et al., 1994	Swedish men occupationally exposed	6	1.16 (0.42–2.52)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, routine exposure	7	0.99 (0.40–2.04)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	No trichloroethylene exposure	10	2.5 (0.7–8.9)
	<5 unit-years	8	2.0 (0.5–7.6)
	5–25 unit-years	1	0.4 (0.1–4.0)
	Low-level intermittent	12	2.1 (0.6–7.5)
	Low-level continuous	9	2.2 (0.6–8.1)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Morgan et al., 1998	Aerospace workers in Arizona		
	Any exposure	8	1.32 (0.57–2.60)
	Low exposure	1	0.47 (0.01–2.62)
	High exposure	7	1.78 (0.72–3.66)
Henschler et al., 1995	Male German cardboard manufacturers, employed >1 year	2	3.28 (0.40–11.84)
Greenland et al., 1994	White male US transformer manufacturers, ever exposed	NA	0.99 (0.30–3.32)
Case–Control Studies			
Pesch et al., 2000b	Participants in multiple centers in Germany		
	German job–exposure matrix		
	Trichloroethylene (males)		
	Medium	135	1.1 (0.9–1.4)
	High	138	1.1 (0.9–1.4)
	Substantial	55	1.3 (0.9–1.8)
	Trichloroethylene (females)		
	Medium	28	1.2 (0.8–1.8)
	High	29	1.3 (0.8–2.0)
	Substantial	6	0.8 (0.3–1.9)
	Job task–exposure matrix approach		
	Trichloroethylene (males)		
	Medium	68	1.3 (1.0–1.8)
	High	59	1.1 (0.8–1.5)
	Substantial	22	1.3 (0.8–2.1)
	Trichloroethylene (females)		
	Medium	11	1.3 (0.7–2.6)
	High	7	0.8 (0.4–1.9)
	Substantial	5	1.8 (0.6–5.0)
Dosemeci et al., 1999	Residents of Minnesota	55	1.30 (0.9–1.9)
	Males	33	1.04 (0.6–1.7)
	Females	22	1.96 (1.0–4.0)
Vamvakas et al., 1998	Residents of Germany with long-term exposure	19	10.8 (3.36–34.75)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Finnish workers monitored for exposure	2	1.82 (0.22–6.56)
Cohort Studies—Mortality			
Ruder et al., 2001	Dry-cleaning labor-union workers	5	1.41 (0.46–3.30)
	Tetrachloroethylene only	2	1.73 (0.21–6.25)
	Tetrachloroethylene plus other solvents (likely Stoddard)	3	1.27 (0.26–3.72)
Blair et al., 1990	Members of a dry-cleaning union in St. Louis, MO	2	0.5 (0.1–1.8)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Studies			
Pesch et al., 2000b	Participants in multiple centers in Germany		
	German job–exposure matrix		
	Tetrachloroethylene (males)		
	Medium	154	1.4 (1.1–1.7)
	High	119	1.1 (0.9–1.4)
	Substantial	50	1.4 (1.0–2.0)
	Tetrachloroethylene (females)		
	Medium	12	0.7 (0.4–1.3)
	High	19	1.1 (0.7–1.9)
	Substantial	4	0.7 (0.3–2.2)
	Job task–exposure matrix approach		
	Tetrachloroethylene (males)		
	Medium	44	1.2 (0.9–1.7)
	High	39	1.1 (0.7–1.5)
	Substantial	15	1.3 (0.7–2.3)
	Tetrachloroethylene (females)		
	Medium	8	2.2 (0.9–5.2)
	High	6	1.5 (0.6–3.8)
	Substantial	3	2.0 (0.5–7.8)
Dosemeci et al., 1999	Residents of Minnesota	50	1.07 (0.7–1.6)
	Males, ever exposed	42	1.12 (0.7–1.7)
	Females, ever exposed	8	0.82 (0.3–2.1)
Schlehofer et al., 1995	Residents of Germany		
	Tetrachloroethylene and tetrachlorocarbonate, exposed >5 years	27	2.52 (1.23–5.16)
Mandel et al., 1995	International renal cell carcinoma cases		
	Dry-cleaning industry, ever employed	8	0.9 (0.3–2.4)
	Dry-cleaning solvents, ever exposed	245	1.4 (1.1–1.7)
	1–7 years	70	1.2 (0.9–1.8)
	8–25 years	98	1.7 (1.2–2.4)
	26–60 years	75	1.2 (0.9–1.8)
Mellemgaard et al., 1994	Residents of Denmark, employed >10 years before as dry cleaners		
	Males	2	2.3 (0.2–27)
	Females	2	2.9 (0.3–33)
McCredie and Stewart, 1993	Residents of New South Wales, ever employed in dry-cleaning industry		
	Renal	16	2.49 (0.97–6.35)
	Renal pelvis	8	4.68 (1.32–16.56)
Aschengrau et al., 1993	Residents of upper Cape Cod, MA		
	Any exposure	6	1.23 (0.40–3.11)
	Low exposure	6	1.36 (0.45–3.45)
Asal et al., 1988	Female residents of Oklahoma, usual dry-cleaning occupation	NA	8.7 (0.9–81.3)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	27	1.2 (0.7–1.9)
	Medium or high exposure	12	1.3 (0.7–2.4)
Toluene			
Cohort Studies—Mortality			
Wiebelt and Becker, 1999	Male German rotogravure printers, employed >1 year	2	0.49 (0.06–2.34)
Walker et al., 1993	Shoe manufacturers in two plants in Ohio, potentially exposed to toluene and other solvents		
	Total	9	1.36 (0.62–2.59)
	Males	6	1.71 (0.62–3.73)
	Females	3	0.97 (0.20–2.84)
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	17	0.9 (0.5–1.5)
	Medium or high exposure	8	1.0 (0.5–2.1)
Xylene			
Case–Control Study			
Gérin et al., 1998	Male residents of Montreal, Canada		
	Low exposure	17	1.0 (0.6–1.7)
	Medium or high exposure	6	1.0 (0.4–2.4)
Isopropyl Alcohol			
Cohort Study—Mortality			
Alderson and Rattan, 1980	Male UK isopropyl manufacturers, employed >1 year	2	6.45 (0.78–23.29)[a]
Unspecified Mixtures of Organic Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Finnish workers monitored for exposure		
	Halogenated hydrocarbons	7	0.89 (0.36–1.82)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, routine exposure	14	0.81 (0.44–1.36)
	Years exposed		
	<1	11	1.54 (0.74–3.20)
	1–4	19	1.08 (0.58–2.01)
	≥5	14	0.41 (0.20–0.82)
Steenland and Palu, 1999	US painters and other union members		
	Painters	100	1.06 (0.86–1.29)
	20 years since membership	71	0.97 (0.76–1.22)
	Nonpainters	21	0.77 (0.48–1.18)
	20 years since membership	12	0.67 (0.34–1.17)
Fu et al., 1996	Shoe-manufacturing workers		
	English workers:		
	Probable solvent exposure	1	0.25 (0.01–1.37)
	High solvent exposure	0	—

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Florence workers:		
	Probable solvent exposure	3	3.53 (0.73–10.31)
	High solvent exposure	3	4.00 (0.83–11.69)
Greenland et al., 1994	White male US transformer-assembly workers		
	Solvents, ever exposed	NA	1.64 (0.49–5.50)
Poole et al., 1993	Male US petroleum-refinery workers		
	Aromatic hydrocarbons, ever exposed	80	0.95 (0.50–1.80)
	Chlorinated solvents, ever exposed	12	0.69 (0.32–1.50)
Walker et al., 1993	Shoe-manufacturing workers in Ohio, potentially exposed	9	1.36 (0.62–2.59)
	Males	6	1.71 (0.62–3.73)
	Females	3	0.97 (0.20–2.84)
Garabrant et al., 1988	Aircraft-manufacturing workers in California	12	0.93 (0.48–1.64)
Matanoski et al., 1986	US painters and allied tradesmen, union members	38	1.28 (0.91–1.76)
Morgan et al., 1981	Male US paint and coatings manufacturers, employed >1 year	5	0.39
Case–Control Studies			
Pesch et al., 2000b	Residents of multiple centers in Germany		
	Painters or dyers, males, duration of exposure:		
	Medium	12	1.6 (0.8–3.0)
	Long	10	1.4 (0.7–2.8)
	Very long	5	2.3 (0.8–6.8)
	Job–exposure matrix, organic solvents:		
	Males, substantial exposure	38	1.6 (1.1–2.3)
	Females, substantial exposure	2	0.3 (0.1–1.3)
	Job task–exposure matrix, solvents:		
	Males, substantial exposure	33	1.5 (1.0–2.3)
	Females, substantial exposure	10	2.1 (1.0–4.4)
Dosemeci et al., 1999	Residents of Minnesota		
	Solvents, ever exposed	126	1.16 (0.9–1.5)
	Males	91	0.93 (0.7–1.3)
	Females	35	2.29 (1.3–4.2)
Schlehofer et al., 1995	Residents of Germany		
	Tetrachloroethylene and tetrachlorocarbonate, exposed >5 years	27	2.52 (1.23–5.16)
Mellemgaard et al., 1994	Residents of Denmark		
	Solvents, exposed >10 years before		
	Males	50	1.5 (0.9–2.4)
	Females	16	6.4 (1.8–23.0)
McCredie and Stewart, 1993	Residents of New South Wales, ever exposed to solvents		
	Renal	109	1.54 (1.11–2.14)
	Renal pelvis	24	1.40 (0.82–2.40)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Partanen et al., 1991	Residents of Finland Nonchlorinated solvents, males exposed >5 years	9	3.46 (0.91–13.2)
Harrington et al., 1989	Residents of the UK Solvents, ever exposed	8	1.0 (0.2–4.9)
Sharpe et al., 1989	Residents of Canada Organic solvents, regular exposure	33	1.68 (0.89–3.18)
Asal et al., 1988	Residents of Oklahoma Painting or paint manufacturing, usual occupation	22	1.3 (0.7–2.6)
Jensen et al., 1988	Residents of Denmark Painter or paint manufacturing, ever employed	10	1.8 (0.7–4.6)

NOTE: NA = not available.
[a]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.

BRAIN AND OTHER CENTRAL NERVOUS SYSTEM CANCERS

Description of Case–Control Studies

Three case–control studies of brain cancer were identified. They included different histologic types of brain cancer: astrocytic (Heineman et al., 1994; Thomas et al., 1987), gliomas (Rodvall et al., 1996), and unspecified brain cancers (Paulu et al., 1999). Occupational exposure information was obtained from next of kin (Heineman et al., 1994; Thomas et al., 1987) or from subjects (Rodvall et al., 1996), and in a study of tetrachloroethylene in drinking water the exposure information was based on water quality data (Paulu et al., 1999). In two studies, industrial hygienists attributed exposure to specific solvents on the basis of their own expertise and information provided by subjects (Rodvall et al., 1996; Thomas et al., 1987), and a job–exposure matrix was used in an updated analysis of the Thomas and colleagues' study (1987) (Heineman et al., 1994) (see Table 6.31).

Epidemiologic Studies of Exposure to Organic Solvents and Brain and Central Nervous System Cancers

Most studies found null associations when investigating the relationship between trichloroethylene and risk of brain and other CNS cancers, including studies of workers biologically monitored for exposure (SIR = 1.09, 95% CI = 0.50–2.07) (Anttila et al., 1995), of workers in the aircraft and aerospace industries (Blair et al., 1998: SMR = 0.8, 95% CI = 0.2–2.2; Boice et al., 1999: SMR = 0.54, 95% CI = 0.15–1.37; Morgan et al., 1998: SMR = 0.55, 95% CI = 0.15–1.40), and of workers in transformer assembly (OR = 0.93, 95% CI = 0.32–2.69) (Greenland et al., 1994).

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TABLE 6.31 Description of Case–Control Studies of Brain and Central Nervous System Cancers and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Thomas et al., 1987	White, male cases, age 30 years or more, identified from death certificates in southern Louisiana, northern New Jersey, and Philadelphia in 1978–1981; deceased controls from other causes collected in the same fashion, matched for age, year of death, and study area (see also Heineman et al., 1994) Response rates (next-of-kin): 74% of cases, 63% of controls	300 astrocytic brain tumors	386	Organic solvents	In-person interview of next of kin with structured questionnaire to assess lifetime occupational history (job titles); probability of exposure determined by industrial hygienist assessment	Maximum likelihood estimate	Age at death, cigarette smoking, alcoholism, ethnicity, education
Heineman et al., 1994	See above, Thomas et al., 1987 Response rates (next-of-kin): 74% of cases, 63% of controls	Same cases as above	320	Trichloroethylene Tetrachloroethylene Methylene chloride Chloroform Organic solvents	In-person interview of next of kin with structured questionnaire to assess lifetime occupational history (job titles); probability of exposure to six chlorinated hydrocarbons determined with job–exposure matrixes	Logistic regression	Age, study area
Rodvall et al., 1996	Cases, age 25–74 years, reported to the Regional Cancer Registry among residents of the catchment area of the Uppsala University Hospital in Sweden, with histologic confirmation; controls selected from parish records and matched for sex and age Response rates: 79% of cases, 82% of controls	151 brain gliomas	343	Trichloroethylene Benzene Toluene Xylene Solvents	Self-reported occupational history (job titles) and exposure to specific agents (self-reports) reviewed by occupational hygienist and to assess probability of exposure to specific agents	Multiple logistic regression	Sex, age, population density

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Paulu et al., 1999	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from the records of HCFA and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 79% of cases, 76% of HCFA controls, 74% of RDD controls, 79% of next of kin of deceased controls	36 brain	703	Tetrachloroethylene	Exposure dose estimated in areas of contaminated drinking water, accounting for location and years of residence, water flow, pipe characteristics	Multiple logistic regression	Age at diagnosis, vital status, sex, occupational exposure to solvents; specific cancer risk factors controlled in respective analyses

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing.

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Three studies reported positive associations. Ritz (1999) found a 27% increase in mortality in US uranium processing plant workers (SMR = 1.27, 95% CI = 0.66–2.22) and found that relative risks increased with duration as well as with level of exposure to trichloroethylene. Heineman and colleagues (1994), in a case–control study of astrocytic brain cancer, found no increases in relative risk of brain cancer (OR = 1.1, 95% CI = 0.8–1.6), although relative risks increased with duration of exposure among subjects whose exposures were classified as highly probable (2–20 years: OR = 1.1, 95% CI = 0.3–3.7; more than 20 years: OR = 6.1, 95% CI = 0.7–143.5). Rodvall and colleagues (1996) found an increased risk of glioma among men who reported exposure to trichloroethylene (OR = 2.4, 95% CI = 0.9–6.4).

No associations between exposure to tetrachloroethylene or to dry-cleaning solvents and brain or other CNS cancers were found in the three cohort studies reviewed by the committee (Anttila et al., 1995; Blair et al., 1990; Boice et al., 1999). No association was found in the case–control study of contaminated drinking water (Paulu et al., 1999). A 20% increased risk (OR = 1.2, 95% CI = 0.8–1.6) was found in the case–control study by Heineman and colleagues (1994), but the relative risks did not increase with increasing probability of exposure.

Two studies of photographic film-base manufacturing workers showed an increased risk of brain and other CNS cancer deaths (Hearne and Pifer, 1999: SMR = 2.16, 95% CI = 0.79–4.69; Tomensen et al., 1997: SMR = 1.45, 95% CI = 0.40–3.72). In a study of two nuclear facilities, Carpenter and colleagues (1988) found that the risk of CNS cancer increased with increasing years of exposure to methylene chloride (10–20 years of exposure, 10-year latency: OR = 1.8; over 20 years of exposure, 10-year latency: OR = 4.01), but the numbers of cases were too small to form any meaningful inferences. In contrast, Heineman and colleagues (1994) found that the risk of astrocytic brain cancer increased with the probability of exposure (medium probability: OR = 1.6, 95% CI = 0.8–3.0; high probability: OR = 2.4, 95% CI = 1.0–5.9) and that risk increased with duration of exposure among subjects with high probability of exposure to methylene chloride (2–20 years: OR = 1.8, 95% CI = 0.6–6.0; over 20 years: OR = 6.1, 95% CI 1.1–43.8).

Yin and colleagues (1996a) studied benzene-exposed workers in China and reported a 30% increase in the risk of malignant brain tumors and benign tumors of the brain and unspecified CNS (RR = 1.3, 95% CI = 0.5–4.1). When levels of exposure to benzene were incorporated into a second analysis (Hayes et al., 1996), risk did not increase with increasing cumulative exposure. In a cohort study of women in Shanghai, China, with high probability of exposure to benzene, Heineman and colleagues (1995) found an 80% excess incidence of brain cancer (SIR = 1.8, 95% CI = 1.1–2.8); they also found a dose–response relationship between low exposure to benzene and high exposure (SIR = 1.5, 95% CI = 0.6–3.4 for low, and SIR = 1.8, 95% CI = 1.1–2.9 for high). In a cohort of benzene-exposed workers at Monsanto chemical plants, risk among production workers increased with increasing cumulative exposure, and maintenance workers showed a 20% excess risk (SMR = 1.2, 95% CI = 0.4–2.5) (Ireland et al., 1997).

A nested case–control study of transformer-assembly workers showed an increased risk of malignant and unspecified brain tumors (OR = 2.1, 95% CI = 1.0–4.4) (Greenland et al., 1994). The nested case–control study of workers at two nuclear facilities showed no increase in CNS tumors among those exposed to benzene (ever exposed, 10-year latency: OR = 0.57) (Carpenter et al., 1988). In a population-based case–control study of brain gliomas in Sweden (Rodvall et al., 1996), a 450% increase in relative risk was found (OR = 5.5, 95% CI = 1.4–21.3).

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Only a few investigations have examined the relationship between brain and other CNS cancers and other solvents, including xylene, toluene (Anttila et al., 1998; Rodvall et al., 1996), phenol (Dosemeci et al., 1991), diethylene glycol, ethanol, isopropanol (Leffingwell et al., 1983), and chloroform (Heineman et al., 1994). They yielded no strong support of associations with any of these solvents.

Many of the previously described studies also examined the risk of brain and other CNS cancers in relation to unspecified mixtures of organic solvents. Of the cohort studies, only Boice and colleagues (1999) did not show an increased relative risk among aircraft-manufacturing workers in California who were routinely exposed to mixed solvents (SMR = 0.68, 95% CI = 0.36–1.16). The study of women in Shanghai, China, showed an SIR of 2.0 (95% CI = 1.3–3.0) with high probability of exposure to solvent mixtures (Heineman et al., 1995), which was supported by a study of US transformer-assembly workers who were ever exposed to solvents (OR = 2.65, 95% CI = 0.84–8.36) (Greenland et al., 1994). On the basis of probability of exposure to solvents, Heineman and colleagues (1995) observed a dose–response relationship with an SIR of 1.2 (95% CI = 1.0–1.5) for low probability of exposure and 2.0 (95% CI = 1.3–3.0) for high probability. Carpenter and colleagues (1988) also showed an increased relative risk among workers at two nuclear facilities exposed to various solvents (exposed to trichloroethylene, tetrachloroethylene, and methyl chloroform, no latency: OR = 1.76; with 10-year latency: OR = 1.26). Those exposed to toluene, xylene, and methyl ethyl ketone showed an OR of 1.96 with no latency and 1.37 with 10-year latency.

Two case–control studies also showed positive associations between exposure to unspecified mixtures of organic solvents and brain and other CNS cancer. The study by Rodvall and colleagues (1996) showed an OR of 2.6 (95% CI = 1.3–5.2) for brain gliomas among men with self-reported exposure to solvents; the OR for women was 0.4 (95% CI = 0.1–2.0). Among people with astrocytic brain tumors in Louisiana, New Jersey, and Philadelphia, the odds ratios increased with increasing probability of exposure (low probability: OR = 1.1, 95% CI = 0.6–1.7; medium probability: OR = 1.5, 95% CI = 0.8–2.7; high probability: OR = 1.4, 95% CI = 0.9–2.1) and with duration of employment (2–20 years: OR = 1.1, 95% CI = 0.7–1.7; over 20 years: OR = 1.7, 95% CI = 1.1–2.6).

Summary and Conclusion

Although several studies on trichloroethylene exposure and brain and CNS cancers were positive, a number of limitations weakened their support for an association. Of particular concern was the study by Ritz (1999) of uranium processing plant workers who were also exposed to radioactive dust that could have been associated with brain cancer. In addition, most studies had wide CIs associated with the relative risk estimates, and there was a lack of a body of evidence related to specific types of brain cancer. For exposure to tetrachloroethylene and dry-cleaning solvents, most of the studies did not find an association. In contrast, one study on methylene chloride showed a strong association with astrocytic brain cancer (Heineman et al., 1994) but it was not supported by findings from the cohort studies of all types of brain and other CNS cancers.

Two cohort studies (Greenland et al., 1994; Heineman et al., 1995) and one population-based study in Sweden (Rodvall et al., 1996) of brain cancer showed increased risks with exposure to benzene. In the cohort studies, all brain cancers were grouped together; in the case–control study, histologically confirmed cases of glioma were included (Rodvall et al., 1996). There is no likelihood of recall bias in the case–control study by Rodvall and colleagues,

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inasmuch as exposures were attributed by industrial hygienists unaware of the status of subjects. The committee did not believe that any of these studies were subject to strong confounding biases, in that risk factors for brain and other CNS cancer are not well known. A dose–response relationship between brain and other CNS cancers and increasing levels of exposure was supported by two studies: Heineman et al., 1995; Ireland et al., 1997. However, the study by Hayes and colleagues (1996) did not yield a dose–response relationship based on years of exposure to benzene, nor did the nested case–control study by Carpenter and colleagues (1988) support an association with brain or other CNS cancers. Moreover, several studies were based on small numbers of exposed cases. As a result, the committee did not reach a consensus. Some committee members believed that the evidence was limited/suggestive of an association; others believed it was inadequate/insufficient to determine whether an association exists. Additional research will help to clarify whether an association exists between exposure to benzene and the risk of brain and other CNS cancers.

All but one of the studies reviewed by the committee reported positive associations between exposure to solvent mixtures and brain and other CNS cancers, including two that showed a slight dose–response pattern (Heineman et al., 1994, 1995). However, the studies did not examine the same cancer outcomes; some evaluated only brain cancer, others looked at brain and other CNS cancers together, and still others evaluated specific subtypes of brain cancer. Furthermore, the mixtures of solvents were known in some studies and unspecified in others. Given those concerns and the consistently positive findings, the committee could not reach a consensus; the evidence was neither wholly inadequate/insufficient to determine whether an association exists nor wholly limited/suggestive.

Table 6.32 identifies the key studies and relevant data points reviewed by the committee in drawing its conclusions. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the solvents under review, other than benzene, and brain or other central nervous system cancers.

TABLE 6.32 Selected Epidemiologic Studies—Brain and Central Nervous System Tumors and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Anttila et al., 1995	Biologically monitored workers in Finland		
	Entire period since first measurement	9	1.09 (0.50–2.07)
	0–9 years	0	— (0–1.26)
	10–19 years	8	2.00 (0.86–3.93)
	20+ years	1	0.76 (0.02–4.26)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	4	0.54 (0.15–1.37)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Ritz, 1999	White male US uranium-processing plant workers		
	Trichloroethylene, cutting fluids, or kerosene	12	1.27 (0.66–2.22)
	Trichloroethylene—light exposure		
	>2 years, no latency	6	1.81 (0.49–6.71)
	>2 years, 15-year latency	4	2.29 (0.42–12.5)
	>5 years, no latency	3	1.32 (0.28–6.17)
	>5 years, 15-year latency	3	5.41 (0.87–33.9)
	Trichloroethylene—moderate exposure		
	>2 years, no latency	1	3.26 (0.37–28.9)
	>2 years, 15-year latency	1	6.94 (0.66–73.1)
	>5 years, no latency	1	4.52 (0.49–41.5)
	>5 years, 15-year latency	1	14.4 (1.24–167.0)
Blair et al., 1998	Male aircraft-maintenance workers in Utah	11[a]	0.8 (0.2–2.2)
	<5 unit-years	3	2.0 (0.2–19.7)
	5–25 unit-years	4	3.9 (0.4–34.9)
	>25 unit-years	1	0.8 (0.1–13.2)
Morgan et al., 1998	Aerospace workers in Arizona, employed >6 months	4	0.55 (0.15–1.40)
Greenland et al., 1994	White male US transformer-assembly workers, ever exposed	NA	0.93 (0.32–2.69)
Case–Control Studies			
Rodvall et al., 1996	Hospital catchment-area residents of Sweden, ever exposed (gliomas)	NA	2.4 (0.9–6.4)
Heineman et al., 1994	Male residents of Louisiana, New Jersey, and Philadelphia (astrocytic brain tumors)		
	Ever exposed	128	1.1 (0.8–1.6)
	Low probability	67	1.1 (0.7–1.7)
	Medium probability	42	1.1 (0.6–1.8)
	High probability	12	1.1 (0.5–2.8)
	Duration of employment		
	2–20 years	7	1.1 (0.3–3.7)
	21+ years	5	6.1 (0.7–143.5)
Tetrachloroethylene and Dry-cleaning Solvents			
Cohort Study—Incidence			
Anttila et al., 1995	Biologically monitored workers in Finland, ever exposed	2	1.15 (0.14–4.15)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	2	0.59 (0.07–2.14)
Blair et al., 1990	Dry-cleaning union members in Missouri	1	0.2 (0.0–1.2)
Case–Control Studies			
Paulu et al., 1999	Massachusetts residents exposed through public drinking water	3	0.6 (0.1–1.7)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Heineman et al., 1994	Male residents of Louisiana, New Jersey, and Philadelphia (astrocytic brain tumors)		
	Ever exposed	111	1.2 (0.8–1.6)
	Low probability	72	1.3 (0.8–1.9)
	Medium probability	30	0.9 (0.5–1.6)
	High probability	9	1.2 (0.4–3.5)
	Duration of employment		
	2–20 years	71	1.1 (0.7–1.6)
	21+ years	28	1.4 (0.7–2.7)
Methylene Chloride			
Cohort Studies—Mortality			
Hearne and Pifer, 1999	Male US photographic-film base manufacturing workers, employed >1 year	6	2.16 (0.79–4.69)
Tomenson et al., 1997	Male UK photographic-film base manufacturing workers, ever employed	4	1.45 (0.40–3.72)
Carpenter et al., 1988	Workers at two nuclear facilities		
	All workers		
	No latency	29	1.38
	10-year latency	21	1.00
	Workers with moderate or high exposure:		
	>1 and ≤3 years of exposure		
	No latency	2	1.19
	10-year latency	0	—
	>3 and ≤10 years of exposure		
	No latency	3	1.33
	10-year latency	2	0.83
	>10 and ≤20 years of exposure		
	No latency	1	0.50
	10-year latency	1	1.80
	>20 years of exposure		
	No latency	1	4.00
	10-year latency	1	4.01
Case–Control Study			
Heineman et al., 1994	Male residents of Louisiana, New Jersey, and Philadelphia (astrocytic brain tumors)		
	Ever exposed	119	1.3 (0.9–1.8)
	Low probability	71	1.0 (0.7–1.6)
	Medium probability	29	1.6 (0.8–3.0)
	High probability	19	2.4 (1.0–5.9)
	Duration of employment		
	2–20 years	9	1.8 (0.6–6.0)
	21+ years	8	6.1 (1.1–43.8)
Benzene			
Cohort Study—Incidence			
Heineman et al., 1995	Women in Shanghai, China		
	Low exposure probability	5	1.6 (0.5–3.7)
	High exposure probability	19	1.8 (1.1–2.8)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Low-level exposure	6	1.5 (0.6–3.4)
	High-level exposure	18	1.8 (1.1–2.9)
	High probability and high-level exposure	16	1.7 (1.0–2.8)
Cohort Studies—Mortality			
Ireland et al., 1997	Benzene-exposed male Monsanto workers		
	Production workers		
	<12 ppm-month	1	1.6 (0.0–8.7)
	12–72 ppm-month	1	1.9 (0.0–10.5)
	≥72 ppm-month	2	4.4 (0.5–15.8)
	Maintenance workers	6	1.2 (0.4–2.5)
Yin et al., 1996a	Chinese factory workers, ever exposed	13	1.3 (0.5–4.1)
Hayes et al., 1996	Benzene-exposed workers in China		
	Cumulative exposure		
	<10 ppm-years	1	0.8
	10–39 ppm-years	3	1.9
	40–99 ppm-years	2	1.3
	100–400 ppm-years	1	0.4
	400+ ppm-years	5	2.3
			p trend = 0.48
Greenland et al., 1994	White male US transformer-assembly workers, ever exposed, high probability	NA	2.1 (1.0–4.4)
Carpenter et al., 1988	Workers at two nuclear facilities, ever exposed		
	No latency	28	0.76
	10-year latency	20	0.57
Case–Control Study			
Rodvall et al., 1996	Hospital catchment-area residents of Sweden, ever exposed (gliomas)	NA	5.5 (1.4–21.3)
Other Specific Organic Solvents			
Cohort Study—Incidence			
Anttila et al., 1998	Finnish workers biologically monitored for exposure to aromatic hydrocarbons		
	Toluene	3	1.09 (0.22–3.18)
	Xylene	3	1.62 (0.33–4.72)
Cohort Studies—Mortality			
Dosemeci et al., 1991	Male US industrial workers exposed to phenol	10	0.7 (0.4–1.4)
Leffingwell et al., 1983	Male workers at a Texas chemical plant, ever exposed (gliomas)		
	Diethylene glycol	11	1.25 (0.48–3.25)[b]
	Ethanol	11	1.19 (0.47–3.01)[b]
	Isopropanol	13	1.73 (0.59–5.07)[b]
Case–Control Studies			
Rodvall et al., 1996	Hospital catchment-area residents of Sweden, ever exposed (gliomas)		
	Toluene	NA	3.4 (0.6–19.3)
	Xylene	NA	3.3 (0.6–18.6)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Heineman et al., 1994	Male residents of Louisiana, New Jersey, and Philadelphia, ever exposed to chloroform (astrocytic brain tumors)		
	All	46	1.0 (0.6–1.6)
	Low probability	30	0.8 (0.5–1.4)
	Medium probability	12	3.2 (0.9–12.0)
	High probability	1	0.2 (0.0–1.8)
Unspecified Mixtures of Organic Solvents			
Cohort Study—Incidence			
Heineman et al., 1995	Women in Shanghai, China		
	Low probability of exposure	89	1.2 (1.0–1.5)
	High probability of exposure	27	2.0 (1.3–3.0)
	Low-level exposure	68	1.7 (1.0–1.6)
	High-level exposure	48	1.5 (1.1–2.0)
	High probability and high-level exposure	24	1.9 (1.2–2.8)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, potential routine exposure	13	0.68 (0.36–1.16)
Greenland et al., 1994	White male US transformer-assembly workers, ever exposed	NA	2.65 (0.84–8.36)
Carpenter et al., 1988	Workers at two nuclear facilities, ever exposed		
	Trichloroethylene, tetrachloroethylene, or methyl chloroform		
	No latency	29	1.76
	10-year latency	21	1.26
	Toluene, xylene, or methyl ethyl ketone		
	No latency	28	1.96
	10-year latency	19	1.37
Case–Control Studies			
Rodvall et al., 1996	Hospital catchment-area residents of Sweden, ever exposed (gliomas)		
	Males	23	2.6 (1.3–5.2)
	Females	2	0.4 (0.1–2.0)
Heineman et al., 1994	Male residents of Louisiana, New Jersey, and Philadelphia (astrocytic brain tumors)		
	Ever exposed	186	1.4 (0.9–1.8)
	Low probability	48	1.1 (0.6–1.7)
	Medium probability	32	1.5 (0.8–2.7)
	High probability	106	1.4 (0.9–2.1)
	Duration of employment		
	2–20 years	80	1.1 (0.7–1.7)
	21+ years	87	1.7 (1.1–2.6)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Thomas et al., 1987	Male workers in the petroleum-refining and chemical-manufacturing industries (astrocytic brain tumors)		
	High exposure to organic solvents	38	1.0
	<5 years	9	0.9
	5–19 years	9	0.6
	≥20 years	14	1.1

NOTE: NA = not available.
[a]Results from the combined early and recent followup cohort.
[b]90% CI.

LYMPHATIC AND HEMATOPOIETIC CANCERS

Issue of Classification

Until recently, the International Classification of Diseases (especially ICD-7 and earlier versions) had rubrics for general types of lymphatic and hematopoietic cancers, including lymphosarcoma and reticulosarcoma (ICD-200), Hodgkin's disease (ICD-201), and lymphatic leukemia (ICD-204). There were no categories for distinguishing specific types of cancers, such as acute leukemia. Thus, in the older epidemiologic studies, all lymphatic and hematopoietic neoplasms were grouped together instead of handled as individual types of cancer (such as Hodgkin's disease) or specific cell types (such as acute lymphocytic leukemia). The amalgamation of these relatively rare cancers would increase the apparent sample size but could result in diluted estimates of effect if the different sites of cancer were not associated in similar ways with the exposures of interest. In addition, before the use of immunophenotyping to distinguish ambiguous diseases, diagnoses of these cancers may have been misclassified; for example, non-Hodgkin's lymphoma (NHL) may have been misclassified as Hodgkin's disease (HD) (Irons, 1992). Misclassification of specific types of cancer, if unrelated to exposure, would have attenuated estimates of relative risk and reduced statistical power to detect associations. When the outcome was mortality, rather than incidence, misclassification would be greater because of the errors in the coding of underlying causes of death on death certificates.

For exposures to organic solvents, the committee reviewed studies that combined all lymphatic and hematopoietic cancers because past exposures were considered substantially higher than the lower permissible exposure limits of today. Given the high exposures of the past, the committee believed that observations of increased risks in some groups of the lymphatic and hematopoietic cancers might be indicative of risk of more specific cancer types. Therefore, the results provided by studies that grouped all the lymphatic and hematopoietic cancers together were used as background information during the committee's deliberations, and the findings from studies with greater specificity of cancer type were used as the primary evidence in drawing conclusions of associations between exposure to organic solvents and NHL, Hodgkin's disease (HD), multiple myeloma (MM), acute and adult leukemia, and myelodysplastic syndromes.

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NON-HODGKIN'S LYMPHOMA

In reviewing the literature on NHL, the committee faced an issue of misclassification or selection bias with respect to the accuracy of diagnosis. As explained at the beginning of this section, past ICD codes did not allow for identification of specific cancer types. As a result, epidemiologists may have grouped NHL cases with other lymphatic and hematopoietic cancers to establish sufficient statistical power. The issue was particularly evident when the literature on exposure to nonspecific solvents was reviewed. When a study did not specifically identify NHL as the cancer type being studied, the committee indicated the diagnosis used by the study authors. All these results are presented at the end of this section.

Description of Case–Control Studies

The characteristics of the case–control studies considered by the committee in drawing its conclusions of association are described below in Table 6.33. Most case–control studies reviewed evaluated NHL specifically (Bernard et al., 1984; Blair et al., 1992; Fabbro-Peray et al., 2001; Fritschi and Siemiatycki, 1996b; Hardell et al., 1994; Holly et al., 1997; Olsson and Brandt, 1988; Scherr et al., 1992; Tatham et al., 1997); others studied lymphohematopoietic cancer (Costantini et al. 2001) or malignant lymphoma (Hardell et al., 1981; Persson and Fredriksson, 1999). All case–control studies included interviews with study subjects concerning occupational history, and some interviews included questions about specific chemical exposures.

Some studies relied on the use of a job–exposure matrix (Blair et al., 1992) or industrial hygienist review of questionnaire responses (Costantini et al., 2001; Fritschi and Siemiatycki, 1996b) to determine exposures, but exposure assessment in most of the studies was based on self-reports (Bernard et al., 1984; Fabbro-Peray et al., 2001; Hardell et al., 1981, 1994; Holly et al., 1997; Olsson and Brandt, 1988; Persson and Frederikson, 1999; Persson et al., 1989, 1993; Scherr et al., 1992). Case–control studies on lymphohematopoietic cancer and exposure to organic solvents that had reasonably good assessments of exposure and a sufficient number of exposed cases include those conducted by Blair and colleagues (1992) and Fritschi and Siemiatycki (1996b).

Epidemiologic Studies of Exposure to Organic Solvents and Non-Hodgkin's Lymphoma

The principal cohort studies that provided information concerning risk of NHL and benzene were the study of Chinese factory workers (Hayes et al., 1997; Yin et al., 1996a,b) and the study of American chemical workers (Wong, 1987a,b). A nested case–control study identified from a cohort of petroleum-distribution workers exposed to benzene at relatively low levels also provided information regarding the association (Schnatter et al., 1996a). Increased relative risks of NHL were found in two analyses in the Chinese study (Hayes et al., 1997: RR = 3.0, 95% CI = 0.9–10.5; Yin et al., 1996a,b: RR = 3.0, 95% CI = 1.0–13.0). Risks increased as the duration of occupational exposure to benzene increased, but not as much as with increasing cumulative exposure (Hayes et al., 1997).

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TABLE 6.33 Description of Case–Control Studies of Non-Hodgkin's Lymphoma and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Hardell et al., 1981	Male cases, age 25–80 years at diagnosis, admitted to the Department of Oncology in Umea, Sweden and diagnosed in 1974–1978 with histologic confirmation; living controls selected from the National Population Register, matched on sex, age, and place of residence; deceased controls selected from the National Registry for Causes of Death, matched for the above and year of death	105	335	Organic solvents	Self-administered questionnaire with possible telephone followup to assess solvent exposure (self-reports)	Unadjusted OR	None
Bernard et al., 1984	Cases identified through registries and clinician reporting among residents of the Yorkshire Health Region, UK, with diagnosis in 1979–1981 and histologic confirmation; controls selected from hospital inpatients, matched for age, sex, and geographic area	158	158	Benzene Solvents	In-person interview to assess occupational history (job titles) and details of solvent and chemical contacts (self-reports)	Maximum likelihood estimate	Sex, age
Olsson and Brandt, 1988	Male cases, age 20–81 years, admitted to the Department of Oncology in Lund, Sweden in 1978–1981, with histologic confirmation; controls selected from previous control groups in studies on Hodgkin's disease and soft-tissue sarcoma	167	130	Solvents	In-person interview with structured questionnaire to assess lifetime occupational exposure history (self-reports)	Logistic regression	Age, herbicides, chlorophenols
Persson et al., 1989	Cases, age 20–80 years, identified in 1964–1986 at the Orebro Medical Centre Hospital, Sweden; controls randomly selected from population registers (see also Persson and Fredriksson, 1999; Persson et al., 1993)	106	275	Trichloroethylene White spirit Solvents	Mailed questionnaire to assess occupational exposures (self-reports)	Unadjusted OR	None

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Blair et al., 1992	White, male cases identified in Iowa through the Iowa State Health Registry in 1981–1983 and in Minnesota through a surveillance network of hospitals in 1980–1982 with histologic confirmation; controls identified through RDD (alive, age 21–64 years), the records of HCFA (alive, age over 65 years), and vital records (deceased), stratified for state, age, and year of death Response rates: 87% of cases, 77% of RDD controls, 79% of HCFA controls, 77% of next-of-kin of deceased controls	622	1,245	Benzene Solvents Paints	In-person interview (direct or proxy) with structured questionnaire to assess lifetime occupational history (job titles); probability of exposure determined by industrial hygienist assessment and job–exposure matrixes	Unconditional logistic regression	Age, state, smoking, family cancer history, respondent status, exposure to pesticides and hair dyes
Scherr et al., 1992	Cases identified from nine hospitals in the Boston metropolitan area in 1980–1982 with histologic confirmation; controls selected from town residency lists, matched for sex, age, town, and precinct of residence	303	303	Benzene Chlorinated solvents	In-person interview or mailed questionnaire to assess lifetime occupational and exposure history (self-reports)	Unadjusted OR	None
Persson et al., 1993	Cases, age 20–80 years, identified in 1975–1984 at the University Hospital in Linkoping, Sweden, with histologic confirmation; controls randomly selected from population registers (see also Persson and Fredriksson, 1999; Persson et al., 1989)	31	204	Trichloroethylene White spirit Solvents	Mailed questionnaire to assess occupational exposures (self-reports)	Logistic regression	Age, other exposures
Hardell et al., 1994	Male cases, age 25–80 years at diagnosis, admitted to the Department of Oncology in Umea, Sweden and diagnosed in 1974–1978 with histologic confirmation; living controls selected from the National Population Register, matched on sex, age, and place of residence; deceased controls selected from the National Registry for Causes of Death, matched for the above and year of death	105	335	Benzene Trichloroethylene White spirit Organic solvents	Self-administered questionnaire with possible telephone followup to assess solvent exposure (self-reports)	Mantel-Haenszel	None

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Fritschi and Siemiatycki, 1996b	Male cases and controls, age 35–70 years, diagnosed in 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed for one of 19 anatomic cancer sites; age-matched, population-based controls were also chosen from electoral lists and RDD Response rates: 83% of cases, 71% of population controls	215	1,066 (533 population controls and 533 randomly selected subjects from the eligible cancer control group)	Benzene Solvents	In-person interviews with segments on work histories (job titles); analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures on semiquantitative scales)	Unconditional logistic regression	Age, proxy status, income, ethnicity
Holly et al., 1997	Male cases identified through the Northern California Cancer Center from hospitals in six counties; controls selected through RDD, and matched for sex, county, and age	312	420	Benzene Chlorinated solvents	In-person interview with structured questionnaire to assess chemical and occupational exposures (self-reports)	Unconditional logistic regression	Age
Tatham et al., 1997	Male cases from the Selected Cancers Study, born in 1929–1953, identified from eight population-based cancer registries in 1984–1988 with histologic confirmation; controls selected through RDD and matched for registry and date of birth Response rates: 88% of cases, 83% of controls	1,048	1,659	Chlorinated hydrocarbons Chemical solvents	Telephone interviews (direct or proxy) with questionnaire to assess work (job titles) and exposure history (self-reports)	Conditional logistic regression	Age at diagnosis, year entering study, ethnicity, education, Jewish religion, marital status, smoking status, service in Vietnam, other medical factors
Persson and Fredriksson, 1999	Cases, age 20–80 years, identified in 1964–1986 at the Orebro Medical Centre Hospital and in 1975–1984 at the University Hospital in Linkoping, Sweden, with histologic confirmation; controls randomly selected from population registers (see also Persson et al., 1989, 1993)	199	479	Benzene Trichloroethylene White spirit Solvents	Mailed questionnaire to assess occupational exposures (self-reports)	Mantel-Haenszel	Age, sex

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Costantini et al., 2001	Cases, age 20–74 years, identified through periodic hospital survey and diagnosed in 12 regions in Italy in 1991–1993 with histologic confirmation; controls randomly selected from municipal demographic files and the National Health Services files, matched for age and sex Response rates: 88% of cases, 81% of controls	1,450	1,779	Launderers, dry cleaners, pressers Painters Printers	In-person interview (direct or proxy) with standardized and job-specific questionnaires to assess lifetime occupational history and exposure to solvents; probability of exposure further determined by industrial hygienist	Mantel-Haenszel	Age, sex
Fabbro-Peray et al., 2001	Cases, age 18 years or over, identified from hospitals in Languedoc-Roussillon, France and diagnosed in 1992–1995 with histologic confirmation; controls randomly selected from electoral lists	445	1,025	Benzene Dry-cleaning solvents Rubber industry Paints	In-person interviews to assess occupational history (job titles) and exposure to specific chemicals (self-reports)	Unconditional logistic regression	Age, sex, education, urban setting

NOTE: HCFA = Health Care Financing Administration; RDD = random-digit dialing.

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The US chemical-worker study (Wong, 1987a,b) had only five exposed cases. It showed a weak association with continuous exposure (SMR = 1.13, 95% CI = 0.23–3.30) and no increase in risk with increasing cumulative exposure. The authors examined duration of exposure categorized, but there was only one exposed case per category. In the study of petroleum distributors, with eight exposed cases (Schnatter et al., 1996a), relative risks did not increase with increasing levels of exposure. Wilcosky and colleagues (1984) found a 3-fold risk among rubber-plant workers (OR = 3.0; the authors did not provide CIs, and the committee was not able to calculate them), and Bond and colleagues (1986) in a study of chemical workers found about a 100% increase in mortality (MSR = 1.99, 95% CI = 0.24–7.22). Another cohort study of benzene-exposed oil-refinery workers (Tsai et al., 1983) reported no exposed cases.

Among the case–control studies in which the association between exposure to benzene and NHL was assessed, increased risks were found in the studies by Fabbro-Peray and colleagues (2001) (OR = 2.0, 95% CI = 1.1–3.9); odds ratios increased with duration of exposure. Blair and colleagues (1992) found increased odds ratios for "higher" exposures (OR = 1.5, 95% CI = 0.7–3.1), and Hardell and colleagues (1994) found very large excess risks associated with self-reported exposure to benzene (OR = 28, 95% CI = 1.8–730). No associations were found in several other small case–control studies (Bernard et al., 1984; Fritschi and Siemiatycki, 1996b; Holly et al., 1997; Persson and Fredriksson, 1999; Scherr et al., 1992; Schumacher and Delzell, 1988).

The cohort studies of trichloroethylene-exposed workers and NHL risk include studies of Finnish and Danish biologically monitored workers (Anttila et al., 1995; Hansen et al., 2001), US aircraft and aerospace maintenance and manufacturing workers (Blair et al., 1998, Boice et al., 1999; Morgan et al., 1998), and workers in Sweden (Axelson et al., 1994).

In the Finnish biologic-monitoring study (Anttila et al., 1995), relative risks were increased (SIR = 2.01, 95% CI = 0.65–4.69). In the Danish cohort study (Hansen et al., 2001) of workers biologically monitored for trichloroethylene, a 3.5-fold increased risk of NHL was observed (95% CI = 1.5–6.9). The risk did not increase with increasing levels of exposure, but the statistical power was too low to detect trends.

Increased NHL mortality was found in the US aircraft-maintenance worker study in Utah (Blair et al., 1998) (SMR = 2.0, 95% CI = 0.9–4.6), but it did not increase with cumulative exposure among male and female workers. A 140% increase in risk (OR = 2.4; CI was not provided in the study, and the committee was not able to calculate it) was also found in rubber workers exposed to trichloroethylene (Wilcosky et al., 1984). In the study of aircraft-manufacturing workers in California (Boice et al., 1999), no overall increase in risk was found (SMR = 1.19, 95% CI = 0.65–1.99), but relative risks increased as duration of exposure increased. Axelson and colleagues (1994) found an 85% increase in incidence (SIR = 1.85, 95% CI = 0.38–5.41) among Swedish workers, but no association was found (SMR = 0.96, 95% CI = 0.20–2.81) in the study of aerospace workers in Arizona (Morgan et al., 1998). Two case–control studies in Sweden found increases in NHL risk of 7.2 (95% CI = 1.3–42) (Hardell et al., 1994) and 1.2 (95% CI = 0.5–2.4) (Persson and Fredriksson, 1999) for NHL, but both were based on self-reported exposures.

In several cohort and case–control studies, relative risks of NHL were calculated according to exposure to tetrachloroethylene and dry-cleaning solvents (Anttila et al., 1995; Blair et al., 1990; Boice et al., 1999; Costantini et al., 2001; Fabbro-Peray et al., 2001), toluene or xylene (Anttila et al., 1998; Blair et al., 1998; Svensson et al., 1990; Wilcosky et al., 1984), phenol (Dosemeci et al., 1991), white spirits (Persson and Fredrickson, 1999; Hardell et al.,

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1994), and other specific solvents (Blair et al, 1998; Wilcosky et al., 1984). No consistent positive associations were found between NHL and any of those solvents except white spirits, with which positive associations were found by Persson and Fredrickson (1999) in a Swedish study (OR = 2.6, 95% CI = 1.3–4.7) and by Hardell and colleagues (1994) (OR = 3.2, 95% CI = 1.3–8.3).

The association between exposure to mixtures of organic solvents and NHL has been examined in several studies, many of which are occupational studies, including aircraft manufacturing and maintenance workers (Blair et al., 1998; Boice et al., 1999), uranium-processing plant workers (Ritz, 1999), painters (Blair et al., 1992; Costantini et al., 2001; Lundberg and Milatou-Smith, 1998; Steenland and Palu, 1999), printers (e.g., Costantini et al., 2001; Leon, 1994; Nielsen et al., 1996), and people in several other occupations (such as shoe manufacturing and rubber work). Some studies showed positive associations, and others showed associations close to unity.

Summary and Conclusion

Although there is a substantial body of literature on the association between exposure to specific organic solvents and solvent mixtures and risk of NHL, most studies are based on small numbers of exposed cases. An association between comparatively high relative risks of NHL and exposure to benzene was seen consistently in a number of cohort studies. The studies on exposure to benzene and NHL provide consistently positive findings because the populations or groups had known exposure and there was evidence of exposure–response relationships.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to benzene and non-Hodgkin's lymphoma.

Two cohort studies suggested that there was an increased risk of dying from NHL with exposure to trichloroethylene (Blair et al., 1998; Wilcosky et al., 1984). However, in the rubber worker study, (Wilcosky et al., 1984) they were exposed to numerous other chemicals in addition to trichloroethylene. The Blair study did not demonstrate an exposure–response relationship in examining mortality risk and found no association in relation to incidence risk. One case–control study showed a very strong association (Hardell et al., 1994), but the committee did not feel that it constituted compelling evidence inasmuch there was a high probability that the relative risks were overstated. The evidence between exposure to white spirit and other specific organic solvents was also limited by Hardell and colleagues' study (1994) that used self-reported exposures and lacked credibility owing to possible recall bias. For exposure to unspecified mixtures of solvents, as is the case with many of the other exposures discussed above, statistical fluctuations made it difficult to form any conclusion. Table 6.34 identifies the studies reviewed by the committee in drawing its conclusion regarding association. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the solvents under review, other than benzene, and non-Hodgkin's lymphoma.

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TABLE 6.34 Selected Epidemiologic Studies—Non-Hodgkin's Lymphoma and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Studies—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Male workers, ever exposed	8	3.5 (1.5–6.9)
	Cumulative exposure:		
	Unknown	2	3.6 (0.4–13.0)
	<1080 months, mg/m^3	3	3.9 (0.8–11.0)
	≥1080 months, mg/m^3	3	3.1 (0.6–9.1)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Cumulative exposure, males (incidence)		
	No exposure	5	0.5 (0.2–1.7)
	<5 unit-years	8	0.9 (0.3–2.6)
	5–25 unit-years	4	0.7 (0.2–2.6)
	>25 unit-years	7	1.0 (0.4–2.9)
	Cumulative exposure, females (incidence)		
	No exposure	0	—
	<5 unit-years	1	0.6 (0.1–5.0)
	5–25 unit-years	0	—
	>25 unit-years	2	0.9 (0.2–4.5)
Anttila et al., 1995	Finnish workers exposed to halogenated hydrocarbons	8	1.81 (0.78–3.56)
	Exposure level		
	<100 μmol/L	5	2.01 (0.65–4.69)
	100 + μmol/L	2	1.40 (0.17–5.04)
Axelson et al., 1994	Swedish workers	5	1.56 (0.51–3.64)
	≥2 years of exposure and 10-year latency	3	1.85 (0.38–5.41)
	49 mg/L	2	1.64 (0.20–5.92)
	50–99 mg/L	0	—
	100+ mg/L	1	8.33 (0.22–46.43)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Trichloroethylene, ever exposed (routine)	14	1.19 (0.65–1.99)
	Years of exposure (routine or intermittent)		
	<1	7	0.74 (0.32–1.72)
	1–4	10	1.33 (0.64–2.78)
	≥5	14	1.62 (0.82–3.22)
Blair et al., 1998	Aircraft-maintenance workers in Utah, ever exposed	28	2.0 (0.9–4.6)
	Cumulative exposure, males (mortality)		
	No exposure	11	1.6 (0.5–4.5)
	<5 unit-years	10	1.8 (0.6–5.4)
	5–25 unit-years	6	1.9 (0.6–6.3)
	>25 unit-years	5	1.1 (0.3–3.8)
	Cumulative exposure, females (mortality)		
	No exposure	2	2.0 (0.3–12.2)
	<5 unit-years	3	3.8 (0.8–18.9)
	5–25 unit-years	0	—
	>25 unit-years	4	3.6 (0.8–16.2)
	Exposure levels (males)		
	Low-level intermittent	15	1.5 (0.5–4.3)
	Low-level continuous	12	1.8 (0.6–5.2)
	Frequent peaks	9	1.5 (0.5–4.4)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Exposure levels (females)		
	Low-level intermittent	4	3.9 (0.8–17.7)
	Low-level continuous	2	3.4 (0.5–21.7)
	Frequent peaks	5	3.8 (0.9–16.2)
Morgan et al., 1998	Aerospace workers in Arizona		
	Trichloroethylene-exposed subcohort		
	Lymphosarcoma and reticulosarcoma	3	0.96 (0.20–2.81)
	All other lymphopoietic tissue	11	1.01 (0.51–1.81)
Wilcosky et al., 1984	Male US rubber-industry workers, exposed >1 year	3	2.4
Case–Control Studies			
Persson and Fredriksson, 1999	Residents of Sweden		
	1+ years exposed, latency 5–45 years	16	1.2 (0.5–2.4)
Hardell et al., 1994	Male residents of Sweden		
	Ever exposed	4	7.2 (1.3–42)
Benzene			
Cohort Studies—Incidence			
Hayes et al., 1997	Chinese factory workers	16	3.0 (0.9–10.5)
	Exposed workers, year of hire		
	<1972	15	4.1
	≥1972	1	0.5
	Exposed workers, average ppm		
	<10	7	2.7 (0.7–10.6)
	10–24	2	1.7 (0.3–10.2)
	≥ 25	7	4.7 (1.2–18.1)
	Exposed workers, duration		
	<5 years	1	0.7 (0.1–7.2)
	5–9 years	4	3.3 (0.7–14.7)
	≥10 years	11	4.2 (1.1–15.9)
	Exposed workers, cumulative exposure		
	<40 ppm-years	6	3.3 (0.8–13.1)
	40–99 ppm-years	1	1.1 (0.1–11.1)
	≥100 ppm-years	9	3.5 (0.9–13.2)
Yin et al., 1996a,b	Chinese factory workers, ever exposed	17	3.0 (1.0–13.0)
Cohort Studies—Mortality			
Schnatter et al., 1996a	Male Canadian petroleum-distribution workers		
	0.00–0.49 ppm-years	4	1.00
	0.50–7.99 ppm-years	3	1.21 (0.16–8.07)
	8.00–19.99 ppm-years	1	1.14 (0.02–22.1)
	20–219.8 ppm-years	0	0.0 (0.0–27.6)
Wong, 1987a,b	Male US chemical workers	5	0.91 (0.29–2.11)
	Continuously exposed	3	1.13 (0.23–3.30)
	Continuous exposure by duration		
	<5 years	1	0.65
	5–14 years	1	1.56
	≥15 years	1	2.18

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Cumulative exposure		
	<180 ppm-months	3	2.57 (0.24–3.41)
	180–719 ppm-months	3	1.61 (0.38–5.45)
	≥720 ppm-months	1	1.34 (0.19–4.14)
			p-trend = 0.71
Bond et al., 1986	Male US chemical workers		
	Lymphosarcoma and reticulosarcoma		
	Entire cohort	2	1.80 (0.22–6.57)
	Cohort less those exposed to arsenic, asbestos, or high levels of vinyl chloride	2	1.99 (0.24–7.22)
	Other lymphatic tissue		
	Entire cohort	1	0.76 (0.02–4.29)
	Cohort less those exposed to arsenic, asbestos, or high levels of vinyl chloride	1	0.84 (0.02–4.64)
Wilcosky et al., 1984	Male US rubber-industry workers, exposed >1 year	6	3.0
Tsai et al., 1983	Texas refinery workers		
	1+ years employment in benzene areas		
	All lymphopoietic cancer	0	—
Case–Control Studies			
Fabbro-Peray et al., 2001	Residents of France, ever exposed	22	2.0 (1.1–3.9)
	≤15 years exposed	9	1.7 (0.7–4.3)
	>15 years exposed	13	2.4 (0.9–5.9)
Persson and Fredriksson, 1999	Residents of Sweden		
	1+ years exposed, latency 5–45 years	3	0.8 (0.1–3.8)
Holly et al., 1997	Male residents of San Francisco Bay Area		
	<10 hours of exposure	294	1.0
	10+ hours of exposure	17	1.2 (0.62–2.4)
Fritschi and Siemiatycki, 1996b	Male residents of Montreal		
	Nonsubstantial	20	0.7 (0.4–1.1)
	Substantial	6	0.8 (0.3–2.1)
Hardell et al., 1994	Male residents of Sweden, ever exposed	3	28 (1.8–730)
Blair et al., 1992	Male residents of Iowa and Minnesota		
	Potential exposure	153	1.1 (0.9–1.4)
	Lower intensity	141	1.1 (0.8–1.4)
	Higher intensity	12	1.5 (0.7–3.1)
Scherr et al., 1992	Residents of Boston, MA, ever exposed	4	1.2 (0.5–2.6)
Schumacher and Delzell, 1988	Residents of North Carolina		
	Occupational exposure (ever):		
	White males	56	0.77 (0.56–1.07)
	Black males	10	0.94 (0.47–1.87)
Bernard et al., 1984	Residents of Yorkshire, England, benzene use		
	Males	NA	0.49 (0.21–2.00)
Other Specific Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1998	Finnish workers monitored for exposure to solvents		
	Toluene or xylene, all years	3	1.18 (0.24–3.45)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Anttila et al., 1995	Finnish workers biologically monitored for halogenated hydrocarbons		
	Tetrachloroethylene	3	3.76 (0.77–11.0)
	1,1,1-Trichloroethane	1	3.87 (0.10–21.5)
Svensson et al., 1990	Male rotogravure-plant workers in Sweden		
	Toluene		
	All exposed	1	0.33 (0.01–1.86)
	≥5 years of exposure, >10-year latency	1	0.52 (0.01–2.91)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Tetrachloroethylene, ever exposed (routine)	8	1.70 (0.73–3.34)
	Years of exposure (routine or intermittent)		
	<1	4	1.25 (0.43–3.57)
	1–4	6	1.11 (0.46–2.70)
	≥5	10	1.41 (0.67–3.00)
Blair et al., 1998	Aircraft maintenance workers in Utah		
	Males, ever exposed		
	Stoddard solvent	16	1.3 (0.5–3.5)
	Isopropyl alcohol	7	1.8 (0.6–5.8)
	Other alcohols	3	2.1 (0.5–9.0)
	Acetone	6	1.7 (0.5–5.5)
	Toluene	3	1.0 (0.2–4.2)
	Methyl ethyl ketone	4	1.4 (0.4–5.1)
	Methylene chloride	6	3.0 (0.9–10.0)
	Females, ever exposed		
	Stoddard solvent	5	2.4 (0.6–9.9)
	Isopropyl alcohol	2	5.8 (1.0–34.6)
	Other alcohols	0	—
	Acetone	1	1.3 (0.1–12.8)
	Toluene	2	2.2 (0.4–13.1)
	Methyl ethyl ketone	1	1.6 (0.2–15.7)
	Methylene chloride	0	—
Dosemeci et al., 1991	White, male chemical-manufacturing workers		
	Phenol, ever exposed	4	0.4 (0.1–1.1)
Blair et al., 1990	Members of a dry-cleaning union in St. Louis, MO		
	Lymphosarcoma or reticulosarcoma	7	1.7 (0.7–3.4)
	Other lymphatic cancers	4	0.7 (0.2–1.8)
Wilcosky et al., 1984	US rubber-industry workers, exposed >1 year		
	Specialty naphthas	6	1.4
	Xylenes	4	3.7
	Isopropanol	6	2.9
Case–Control Studies			
Costantini et al., 2001	Residents of 12 areas of Italy		
	Launderers, dry cleaners, and pressers	3	1.6 (0.3–9.1)
Fabbro-Peray et al., 2001	Residents of France		
	Dry-cleaning solvents, ever exposed	35	1.0 (0.6–1.6)
Persson and Fredriksson, 1999	Residents of Sweden		
	White spirit, 1+ years exposed, latency 5–45 years	27	2.6 (1.3–4.7)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Hardell et al., 1994	Male residents of Sweden		
	White spirit (ever exposed)	12	3.2 (1.3–8.3)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1998	Biologically monitored Finnish workers		
	Aromatic hydrocarbons, all years	2	0.52 (0.06–1.88)
Lundberg and Milatou-Smith, 1998	Swedish paint-industry workers		
	Male workers, ≤5 years of employment	2	1.0 (0.1–3.4)
Nielsen et al., 1996	Danish lithographer-union members, malignant lymphoma	2	1.5 (0.3–5.0)
Berlin et al., 1995	Swedish workers occupationally exposed to solvents	7	1.9 (0.8–4.0)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	All factory workers	137	0.94 (0.79–1.11)[a]
	Mixed solvents, ever exposed (routine)	29	1.02 (0.68–1.47)
	Years of exposure (routine or intermittent)		
	<1	9	0.77 (0.37–1.62)
	1–4	20	0.79 (0.45–1.39)
	≥5	52	1.01 (0.64–1.61)
Ritz, 1999	White male US uranium-processing plant workers, employed >3 months	8	1.71 (0.73–3.36)
Steenland and Palu, 1999	US painter union members		
	Painters (all members)	137	1.06 (0.89–1.25)
	Painters (20 years since first union membership)	110	1.10 (0.91–1.32)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Any solvent, ever exposed		
	Males	31	1.6 (0.6–4.1)
	Females	9	2.8 (0.8–4.5)
	Solvents, unspecified, ever exposed		
	Males	31	1.6 (0.6–4.1)
	Females	9	2.9 (0.8–10.6)
Fu et al., 1996	Shoe-manufacturing workers		
	English cohort	6	0.55 (0.20–1.20)
	Probable solvent exposure	2	0.54 (0.07–1.96)
	High solvent exposure	0	—
	Florence cohort	2	1.06 (0.13–3.82)
	Probable solvent exposure	2	2.44 (0.30–8.81)
	High solvent exposure	2	2.74 (0.33–9.90)
Hunting et al., 1995	Male vehicle mechanics in Washington, DC		
	Solvents or fuels, high exposure (lymphatic and hematopoietic)	3	4.22 (0.87–12.34)
	Solvents or fuels, high exposure (other neoplasms of lymphatic and hematopoietic)	1	2.57 (0.06–14.27)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Leon, 1994	Male trade-union members in the British printing industry		
	Machine managers	2	1.21 (0.15–4.37)
	Compositors	4	1.17 (0.32–2.99)
	Machine assistants	4	2.16 (0.59–5.54)
	Publishing-room men	2	2.68 (0.32–9.68)
Wong et al., 1993	US gasoline-distribution workers		
	Land-based terminal cohort (cancer of other lymphatic tissue)	18	0.92 (0.54–1.45)
	Marine-based cohort (cancer of other lymphatic tissue)	11	0.73 (0.39–1.25)
Walker et al., 1993	Shoe-manufacturing workers in Ohio, employed >1 month	5	0.75 (0.24–1.77)
Teta et al., 1992	Male workers at ethanol and isopropanol production plants in Texas		
	All workers (South Charlestown plant)	5	5.60 (1.8–13.0)
Paci et al., 1989	Shoe-manufacturing plant in Florence, Italy, ever employed		
	Other lymphatic and hematopoietic neoplasms		
	Males	1	0.55 (0.0–3.1)[a]
	Females	1	1.11 (0.0–6.2)[a]
Sorahan et al., 1989	British rubber-industry workers (lymphoid cancers)	50	0.91 (0.68–1.21)[a]
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years		
	Lymphosarcoma and reticulosarcoma	13	0.82 (0.44–1.41)
	Other neoplasms of lymphatic and hematopoetic tissue	5	0.65 (0.21–1.52)
Wilcosky et al., 1984	Male US rubber-industry workers, exposed >1 year		
	Solvent "A" (mixture of toluene and other solvents)	6	2.6
Paganini-Hill et al., 1980	Newspaper web pressmen union members in Los Angeles, CA (other lymphatic and hematopoietic neoplasms)	5	1.29 (0.42–2.99)[a]
Case–Control Studies			
Costantini et al., 2001	Residents of 12 areas of Italy		
	Painters, ever employed	20	1.2 (0.6–2.4)
	Printers, ever employed	11	1.2 (0.6–2.9)
Fabbro-Peray et al., 2001	Residents of France		
	Rubber industry, ever employed	16	1.6 (0.8–3.4)
	Paints, ever exposed	26	0.8 (0.5–1.3)
Persson and Fredriksson, 1999	Residents of Sweden		
	1+ years exposed, latency 5–45 years		
	Solvents	61	1.6 (1.0–2.5)
	Solvents, high intensity	51	1.8 (1.1–2.9)
Holly et al., 1997	Male residents of the San Francisco Bay area		
	Chlorinated solvents		
	<10 hours of exposure	291	1.0
	10+ hours of exposure	20	0.73 (0.41–1.3)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Tatham et al., 1997	Males in US cancer registries		
	Chemical solvents, ever exposed	451	1.10 (0.90–1.30)
	Chlorinated hydrocarbons, ever exposed	49	0.91 (0.62–1.30)
Fritschi and Siemiatycki, 1996b	Male residents of Sweden		
	Nonsubstantial	26	0.6 (0.4–1.0)
	Substantial	48	0.9 (0.6–1.3)
Hardell et al., 1994	Male residents of Sweden		
	Organic solvents		
	All	45	2.4 (1.4–3.9)
	High grade	31	2.9 (1.6–5.6)
	Low grade	14	1.8 (0.8–3.8)
Partanen et al., 1993	Finnish production workers in the wood industry (leukemias and lymphomas pooled)		
	Solvents, ever exposed	4	5.62 (0.99–32.0)
	Solvents, adjusted for formaldehyde	4	5.07 (0.40–63.5)
Blair et al., 1992	Male residents of Iowa and Minnesota		
	Solvents (excluding benzene)		
	Potentially exposed	359	1.1 (0.9–1.4)
	Lower intensity	334	1.1 (0.8–1.4)
	Higher intensity	25	1.4 (0.8–2.5)
	Paints:		
	Potentially exposed	116	1.1 (0.9–1.5)
	Lower intensity	107	1.1 (0.9–1.5)
	Higher intensity	9	1.1 (0.5–2.6)
Scherr et al., 1992	Residents of Boston, MA		
	Chlorinated solvents, ever exposed	24	1.2 (0.8–1.8)
Persson et al., 1989	Residents of Sweden		
	Solvents	33	2.0 (1.2–3.5)[a]
	Solvents, high intensity	27	2.1 (1.2–3.7)[a]
Olsson and Brandt, 1988	Male residents of Sweden		
	Solvent exposure, ever (based on observed cases)	NA	2.0 (1.5–2.6)
	120 months	NA	1.8 (1.2–2.7)
	240 months	NA	3.3 (1.5–7.1)
	360 months	NA	6.0 (1.9–19.0)
Bernard et al., 1984	Residents of Yorkshire, England		
	Occupational solvents (excluding benzene)		
	Males	NA	1.52 (0.70–3.26)
	Females	NA	7.71 (1.24–47.93)
	Solvent use as a hobby, males	NA	1.39 (0.30–6.46)
Hardell et al., 1981	Male residents of Sweden (malignant lymphoma)		
	Organic solvents, low grade	10	1.2 (0.5–2.6)
	Organic solvents, low and high grade	50	2.4 (1.5–3.8)
	Solvents, phenoxy acids, or chlorophenols	23	8.5 (4.2–17.2)

NOTE: NA = not available.

[a]95% CI was calculated by the committee with standard methods from the observed and expected numbers presented in the original papers.

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HODGKIN'S DISEASE

Description of Case–Control Studies

The characteristics of the case–control studies considered by the committee in drawing its conclusion regarding association are described in Table 6.35. All case–control studies of HD reviewed by the committee included interviews with study subjects about occupational history; some also inquired about specific chemical exposures. Although some studies relied on industrial hygienist review of questionnaire responses (Costantini et al., 2001) to determine exposure, exposure assessment in other studies was based on self-reports (Bernard et al., 1984; Hardell and Bengtsson, 1983; Persson et al., 1989, 1993).

Epidemiologic Studies Regarding Exposure to Organic Solvents and Hodgkin's Disease

Each of the studies of exposure to trichloroethylene reviewed showed an increased risk of HD. However, most studies had small numbers of exposed cases (Anttila et al., 1995; Axelson et al., 1994; Blair et al., 1998; Boice et al., 1999; Morgan et al., 1998; Persson et al., 1993); therefore, the confidence intervals were broad and included unity. The only study showing markedly increased risk was by Persson and colleagues (1989) (OR = 2.8, 95% CI 0.96–7.86).

Two studies provided results on the relationship between exposure to benzene and risk of HD. A cohort study of male chemical-plant workers (Wong, 1987a) who were continuously exposed to benzene did not show any increased risk (SMR = 1.12, 95% CI = 0.14–4.05), and a case–control study among residents in Yorkshire, England (Bernard et al., 1984) also showed no relationship between exposure to benzene and HD (OR = 1.00, 95% CI = 0.50–1.50).

Studies of other specific solvents—including tetrachloroethylene (Blair et al., 1990; Boice et al., 1999), toluene and xylene (Anttila et al., 1998), phenol (Dosemeci et al., 1991), and white spirit (Persson et al., 1989, 1993)—did not show any evidence of increased risk of HD.

The risk of HD associated with exposure to unspecified mixtures of solvents or employment in solvent-related occupations—including aircraft-manufacturing workers, painters, printers, and dry cleaners—was investigated in several cohort and case–control studies. Although several studies yielded positive relative risks, most had considerable statistical variability in their estimates. Only one study (Hardell and Bengston, 1983) showed a risk that was well above the null value; its subjects had concomitant exposure to phenoxy acids and chlorophenols, and exposure to all substances conferred an almost 7-fold excess risk (OR = 6.6, 95% CI 2.4–18.5).

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TABLE 6.35 Description of Case–Control Studies of Hodgkin's Disease and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Hardell and Bengtsson, 1983	Male cases, age 25–80 years at diagnosis, admitted to the Department of Oncology in Umea, Sweden, and diagnosed in 1974–1978 with histologic confirmation; living controls selected from the National Population Register, matched on sex, age, and place of residence; deceased controls selected from the National Registry for Causes of Death, matched for the above and year of death	60	335	Organic solvents	Self-administered questionnaire with possible telephone followup to assess solvent exposure (self-reports)	Mantel-Haenszel	None
Bernard et al., 1984	Cases identified through registries and clinician reporting among residents of the Yorkshire Health Region, UK, with diagnosis in 1979–1981 and histologic confirmation; controls selected from hospital inpatients, matched for age, sex, and geographic area	48	48	Benzene Solvents	In-person interview to assess occupational history (job titles) and details of solvent and chemical contacts (self-reports)	Logistic regression	Sex, age
Persson et al., 1989	Cases, age 20–80 years, identified in 1964–1986 at the Orebro Medical Centre Hospital, Sweden; controls randomly selected from population registers	54	275	Trichloroethylene White spirit Solvents	Mailed questionnaire to assess occupational exposures (self-reports)	Unadjusted OR, Logistic regression	Age, sex, other exposures
Persson et al., 1993	Cases, age 20–80 years, identified in 1975–1984 at the University Hospital in Linkoping, Sweden, with histologic confirmation; controls randomly selected from population registers	31	204	Trichloroethylene White spirit Solvents	Mailed questionnaire to assess occupational exposures (self-reports)	Unadjusted OR, Logistic regression	Age, other exposures
Costantini et al., 2001	Cases, age 20–74 years, identified through periodic hospital survey and diagnosed in 12 regions in Italy in 1991–1993 with histologic confirmation; controls randomly selected from municipal demographic files and the National Health Services files, matched for age and sex Response rates: 88% of cases, 81% of controls	365	1,779	Launderers, dry cleaners, pressers	In-person interview (direct or proxy) with standardized and job-specific questionnaires to assess lifetime occupational history (job titles) and exposure to solvents (self reports); probability of exposure further determined by industrial hygienist	Mantel-Haenszel	Age, sex

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Summary and Conclusion

Overall, the studies reviewed by the committee did not show any persuasive evidence of associations between HD and exposure to specific solvents or solvent mixtures. Although many of the studies of exposure to mixtures of solvents yielded increased risk estimates, there was considerable statistical variability in them. The incidence of HD is low, and most studies had small numbers of exposed cases to evaluate. Having such small numbers may lead to spuriously increased relative risks when the null hypothesis of no association is true. That limitation is reflected in the wide CIs observed in most of the studies. The lack of specific or validated exposure-assessment information and the impact of bias are other limitations that the committee considered in drawing its conclusion. Table 6.36 identifies the key studies reviewed for each exposure and the data points evaluated by the committee. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review and Hodgkin's disease.

TABLE 6.36 Selected Epidemiologic Studies—Hodgkin's Disease and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Anttila et al., 1995	Biologically monitored workers in Finland	3	1.70 (0.35–4.96)
	<100 µmol/L	2	2.00 (0.24–7.22)
	≥100 µmol/L	1	1.83 (0.05–10.2)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California, potential routine exposure	4	2.77 (0.76–7.10)
Blair et al., 1998	Aircraft-maintenance workers in Utah, employed >1 year	5	1.4 (0.2–12.0)
Morgan et al., 1998	Aerospace workers in Arizona		
	All exposed	1	0.60 (0.02–3.35)
	Low exposure	1	1.55 (0.04–8.64)
	High exposure	0	—
Axelson et al., 1994	Biologically monitored male workers in Sweden	1	1.07 (0.03–5.95)
Case–Control Study			
Persson et al., 1989	Residents of Sweden, exposed >1 year	7	2.8 (0.96–7.86)[a]
Benzene			
Cohort Study—Mortality			
Wong, 1987a,b	US male chemical-plant workers	3	0.81 (0.16–2.36)
	Benzene, continuously exposed	2	1.12 (0.14–4.05)
	Not exposed to benzene	1	0.75 (0.19-4.15)
	Duration of exposure, continuously exposed to benzene:		
	<5 years	1	0.88
	5–14 years	1	2.37
	≥15 years	0	—

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–Control Study			
Bernard et al., 1984	Residents of Yorkshire, England	NA	1.00 (0.50–1.50)
Other Specific Organic Solvents			
Cohort Study—Incidence			
Anttila et al., 1998	Biologically monitored workers in Finland (includes HD, NHL, and other lymphohematopoietic cancers)	3	0.78 (0.16–2.28)
	Toluene	3	1.18 (0.24–3.45)
	Xylene		
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Tetrachloroethylene, potential routine exposure	0	—
Dosemeci et al., 1991	US male plant workers		
	Phenol		
	Any exposure	10	1.7 (0.8–3.1)
	No exposure	2	0.5
	Low cumulative exposure	8	2.3
	Medium cumulative exposure	2	0.9
	High cumulative exposure	0	—
Blair et al., 1990	Members of a dry-cleaning union in Missouri		
	Dry-cleaning solvents	4	2.1 (0.6–5.3)
Case–Control Studies			
Persson et al., 1993	Residents of Sweden		
	White spirits, exposed >1 year	4	1.4 (0.36–4.67)[a]
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1998	Biologically monitored workers in Finland		
	Aromatic hydrocarbons	3	1.49 (0.31–4.36)
Anttila et al., 1995	Biologically monitored workers in Finland		
	Halogenated hydrocarbons	3	1.45 (0.30–4.23)
Berlin et al., 1995	Swedish workers occupationally exposed to solvents	2	6.3 (0.8–22.7)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, potential routine exposure	6	1.61 (0.59–3.51)
Ritz, 1999	White male uranium-processing workers in Ohio		
	Ever exposed to solvents	6	2.09 (0.76–4.54)
Steenland and Palu, 1999	Members of the US Painters Union		
	Ever employed as a painter	16	1.30 (0.74–2.11)
	Nonpainter	4	0.54 (0.06–1.93)
	20 years since first union membership	10	1.17 (0.56–2.15)
Walker et al., 1993	Ohio shoe-manufacturing plants, employed >1 month	4	1.12 (0.31–2.88)
Garabrant et al., 1988	Aircraft-manufacturing workers in California, employed >4 years	4	0.73 (0.20–1.88)
Wen et al., 1985	Cohort of male oil refinery workers		
	Total lubricating cohort	1	1.61 (0.04–8.98)
	Other lubricating cohort	1	2.17 (0.28–12.10)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Alderson and Rattan, 1980	Male British workers in dewaxing plants		
	Isopropyl alcohol production-plant workers	0	0.09 (0.0–33.55)[b]
	Methyl ethyl ketone production-plant workers	0	0.10 (0.0–20.50)[b]
Case–Control Studies			
Costantini et al., 2001	Residents in 12 areas of Italy		
	Launderers, dry cleaners, and pressers	1	2.5 (0.3–24.6)
Persson et al., 1993	Residents of Sweden		
	Solvents, high intensity	7	1.8 (0.7–4.6)[c]
Bernard et al., 1984	Residents of Yorkshire, England		
	Solvents (excluding benzene)	NA	0.45 (0.15–1.42)
	Petrol products	NA	1.15 (0.37–3.56)
Hardell and Bengtsson, 1983	Male residents of three counties of Sweden		
	Low-grade exposure (age 25–85 years)	4	1.2 (0.4–3.8)
	High-grade exposure (age 25–85 years)	14	3.0 (1.4–6.1)
	Ever exposed to solvents or phenoxy acids or chlorophenols	7	6.6 (2.4–18.5)

NOTE: NA = not available.
[a]95% CIs were calculated by the committee with standard methods from the observed numbers presented in the original study.
[b]Estimated risk and 95% CIs were calculated by the committee with standard methods from the observed and expected numbers presented in the original study.
[c]90% CI is reported.

MULTIPLE MYELOMA

Description of Case–Control Studies

Table 6.37 describes the two case–control studies that the committee reviewed to assess the association between MM and exposure to organic solvents. Morris and colleagues (1986) evaluated the association between risk of MM and self-reported exposure to 20 chemicals that were included in a standard questionnaire administered to subjects or to family members if a subject was deceased or too ill to be interviewed. Using the same study population, Demers and co-workers (1993) evaluated the association between MM and employment in a variety of occupations and industries. Eriksson and Karlsson (1992) conducted a population-based case–control study in Sweden in which subjects or the next of kin of deceased subjects were interviewed with self-administered questionnaires and by telephone. Occupational and leisure-time exposure to organic solvents was reported by the subjects.

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TABLE 6.37 Description of Case–Control Studies of Multiple Myeloma and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Morris et al., 1986	Cases identified through SEER tumor registries in four geographic areas who were under the age of 80 years and newly diagnosed in 1977–1981; population controls identified through random-digit dialing and a population survey of the four geographic areas Response rates: 89% of cases, 83% of controls	698	1,683	Aldehydes or ketones Aromatic hydrocarbons Chlorinated hydrocarbons Paints or solvents	Interviews with a standardized questionnaire (direct or proxy) to assess occupational history (job titles) and specific exposure agents (self-reports); data obtained directly from 68% of cases and 99% of controls	Mantel-Haenszel	Sex, age, race, study area
Eriksson and Karlsson, 1992	Cases reported to the Swedish Cancer Registry from the four northernmost counties of Sweden in 1982–1986; medical records were reviewed to confirm the diagnosis; for each living case, two controls were identified from the Swedish National Population Registry and cancer controls, and for each deceased case, one control was selected from the National Registry for Causes of Death Response rates: 98.5% of cases, 95.3% of controls	275	275	Organic solvents (occupational and leisure exposure)	Occupational histories (job titles) and specific leisure or work exposures obtained through questionnaire and supplemented by telephone interview (direct or proxy) (self-reports)	Univariate analysis	None
Demers et al., 1993	Same study population as Morris et al., 1986 above.	692	1,683	Painters Printing-machine operators	Same as above; occupations and industries coded according to the 1970 US Census	Mantel-Haenszel	Sex, age, race, study area

NOTE: SEER = Surveillance, Epidemiology, and End Results.

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Epidemiologic Studies of Exposure to Organic Solvents and Multiple Myeloma

The association between MM and exposure to trichloroethylene was evaluated in cohort studies of workers who were monitored biologically for a metabolite of trichloroethylene (SIR = 0.9, 95% CI = 0.01–4.7) (Hansen et al., 2001), in trichloroethylene-production workers (SIR = 0.57, 95% CI = 0.01–3.17) (Axelson et al., 1994), in aircraft-manufacturing workers (SMR = 0.91, 95% CI = 0.34–1.99) (Boice et al., 1999), and in aircraft-maintenance workers (SMR = 1.3, 95% CI = 0.5–3.4) (Blair et al., 1998). In the Blair and colleagues' study (1998), no increases in relative risk with increasing cumulative exposure were found, but women exposed intermittently to trichloroethylene at low levels had an RR of 4.4 (95% CI = 1.0–20.4).

The authors of four cohort studies examined the relationship between exposure to benzene and the risk of MM. Rinsky and colleagues (1987) reported an SMR of 4.09 (95% CI = 1.10–10.47) in the cohort of Pliofilm workers in Ohio. Additional years of followup did not add any cases of MM; with the increased number of person-years of observation, the strength of the association was reduced by about 70% (SMR = 2.91, 95% CI = 0.79–7.45) (Wong, 1995).

Among Monsanto chemical-plant workers who used benzene in various production operations, an RR of 3.23 (95% CI = 0.7–9.4) was observed (Ireland et al., 1997), but no exposure–response pattern was found. A nested case–control study based on a cohort of Canadian petroleum-distribution workers showed an increased risk of MM only when benzene exposures were more than 20 ppm per year (OR = 1.22, 95% CI = 0.07–20.0; two cases) (Schnatter et al., 1996a), but there was no evidence of an exposure trend. In the Chinese study of benzene-exposed workers, no increased risk of MM was found (one exposed case; Yin et al., 1996a,b).

Cohort studies of aircraft workers and aircraft-maintenance workers assessed the association between risk of MM and exposure to solvents, other than trichloroethylene. Boice and colleagues (1999) found no evidence of an association with tetrachloroethylene. Blair and colleagues (1998) reported an increased risk of MM in those ever exposed to toluene (RR_{women} = 5.0, 95% CI = 1.1–23.1), methyl ethyl ketone (RR_{women} = 4.6, 95% CI = 0.9–23.2), or methylene chloride (RR_{men} = 3.4, 95% CI = 0.9–13.2).

A number of cohort and case–control studies were used to examine the association between exposures to unspecified mixtures of organic solvents and risk of MM, including several studies of painters (Boice et al., 1999; Demers et al., 1993; Lundberg and Milatou-Smith, 1998; Steenland and Palu, 1999), aircraft maintenance and manufacturing workers (Blair et al., 1998; Boice et al., 1999), and shoe manufacturers (Fu et al., 1996), all of whom used various solvent mixtures in their occupations. In one study (of shoe-manufacturing workers), benzene was a likely component of the mixtures, but relative risks were not specifically reported (Fu et al., 1996).

In a cohort study of paint manufacturers (Lundberg and Milatou-Smith, 1998), increased mortality from and incidence of MM were observed (SMR = 3.8, 95% CI = 1.0–9.7; SIR = 3.2, 95% CI = 0.9–8.3). Painters were at increased risk (SMR = 1.70, 95% CI = 0.46–4.35) in one study (Boice et al., 1999), but not in a study of painter-union members (SMR = 0.97, 95% CI = 0.75–1.24); it was similar to the risk found for nonpainters (SMR = 0.90, 95% CI = 0.52–1.46) (Steenland and Palu, 1999).

Other studies of MM and exposure to unspecified mixtures of organic solvents were conducted. Blair and colleagues (1998) found a 30% excess MM mortality among men (RR = 1.3, 95% CI = 0.4–3.8) and women (RR = 1.9, 95% CI = 0.4–8.2) exposed to any solvent. An

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increased incidence of MM was found among a cohort of Swedish workers occupationally exposed to solvents (SIR = 2.0, 95% CI = 0.4–5.7) (Berlin et al., 1995). The study by Boice and colleagues (1999) did not show an association (other than in painters) between exposure to mixtures of solvents and risk of MM (SMR = 1.17, 95% CI = 0.95–1.45).

One case–control study (Demers et al., 1993; Morris et al., 1986) showed an increased relative risk of MM among painters. Morris and colleagues (1986) found an 80% increase in incidence of MM among subjects exposed to paints or mixtures of solvents (OR = 1.8, 95% CI = 1.2–2.7). Using the same population, Demers and colleagues (1993) observed a positive exposure–response pattern among painters according to length of employment (less than 10 years: OR = 1.4, 95% CI = 0.6–2.8; 10 years or more duration: OR = 4.1, 95% CI = 1.8–10.4).

Summary and Conclusion

None of the studies yielded persuasive evidence that exposure to trichloroethylene increased the risk of MM. The lack of increased relative risks was observed in the studies on exposure to benzene. Most studies on other specific solvents, such as tetrachloroethylene, toluene, methyl ethyl ketone, or methylene chloride, did not find a positive association, or if they did, they were not supported by other corroborating studies.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to specific solvents under review and multiple myeloma.

For exposure to solvent mixtures, a number of studies on painters found increased risk of MM, including one study that found an increasing risk with increasing years of employment (Demers et al., 1993). Table 6.38 identifies the key studies reviewed for each exposure and the data points evaluated by the committee. Unless indicated in the tables, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to solvents (as observed in studies of painters) and multiple myeloma.

TABLE 6.38 Selected Epidemiologic Studies—Multiple Myeloma and Exposures to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males, ever exposed	1	0.9 (0.01–4.7)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Routine exposure	6	0.91 (0.34–1.99)
	Routine or intermittent		
	<1 year of exposure	3	0.45 (0.13–1.54)
	1–4 years of exposure	8	1.48 (0.64–3.41)
	≥5 years of exposure	3	0.51 (0.15–1.76)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Any exposure (males and females)	14	1.3 (0.5–3.4)
	Males		
	Low level intermittent	4	0.5 (0.1–1.9)
	Low level continuous	4	0.8 (0.2–3.2)
	Frequent peaks	4	0.8 (0.2–3.3)
	Females		
	Low level intermittent	4	4.4 (1.0–20.4)
	Low level continuous	1	2.4 (0.2–24.3)
	Frequent peaks	1	0.9 (0.1–8.9)
	Cumulative exposure, males (mortality)		
	No exposure	10	1.7 (0.5–5.5)
	<5 unit-years	4	1.0 (0.2–4.2)
	5–25 unit-years	2	0.8 (0.1–4.4)
	>25 unit-years	4	1.2 (0.3–4.7)
	Cumulative exposure, females (mortality)		
	No exposure	11	1.0 (0.1–9.9)
	<5 unit-years	2	3.2 (0.5–19.8)
	5–25 unit-years	1	4.3 (0.4–43.4)
	≥25 unit-years	1	1.3 (0.1–13.2)
Axelson et al., 1994	Male workers in Sweden, ever exposed	1	0.57 (0.01–3.17)
Benzene			
Cohort Studies—Mortality			
Ireland et al., 1997	Male US chemical-plant workers		
	Production workers		
	Nonexposed	1	0.5 (0.0–2.8)
	Any exposure	3	3.2 (0.7–9.4)
	<12 ppm-month	0	0.0 (0.0–10.1)
	12–72 ppm-month	2	6.8 (0.8–2.5)
	>72 ppm-month	1	3.7 (0.1–20.1)
Schnatter et al., 1996a	Male Canadian petroleum-distribution workers		
	0.00–0.49 ppm-years	3	1.00
	0.50–7.99 ppm-years	1	0.39 (0.01–5.16)
	8.00–19.99 ppm-years	1	0.60 (0.01–7.83)
	20–219.8 ppm-years	2	1.22 (0.07–20.0)
Yin et al., 1996a,b	Chinese factory workers, ever exposed	1	0.4 (0.0–10.7)
Wong, 1995	Male US Pliofilm workers in Ohio (through 1987)	4	2.91 (0.79–7.45)
	<40 ppm-years	3	3.21 (0.66–9.39)
	40–200 ppm-years	0	0 (0–12.29)
	200–400 ppm-years	0	0 (0–36.89)
	>400 ppm-years	1	25.17 (0.63–139.83)
Rinsky et al., 1987	Male US Pliofilm workers in Ohio (through 1981)	4	4.09 (1.10–10.47)
	<40 ppm-years	3	4.58 (0.92–13.39)
	40–200 ppm-years	0	0
	200–400 ppm-years	0	0
	>400 ppm-years	1	53.47 (0.70–297.53)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Other Organic Solvents			
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Tetrachloroethylene, routine exposure	1	0.40 (0.01–2.25)
	Routine or intermittent exposure		
	<1 year of exposure	1	0.46 (0.06–3.48)
	1–4 years of exposure	4	1.13 (0.38–3.35)
	≥5 years of exposure	1	0.24 (0.03–1.84)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Stoddard solvent		
	Males	96	1.0 (0.3–3.2)
	Females	3	1.6 (0.3–8.2)
	Isopropyl alcohol (males)	4	1.5 (0.4–6.4)
	Trichloroethane (females)	2	13.2 (2.2–80.4)
	Acetone		
	Males	4	1.6 (0.4–6.7)
	Females	2	3.8 (0.6–23.8)
	Toluene		
	Males	2	0.9 (0.2–4.8)
	Females	4	5.0 (1.1–23.1)
	Methyl ethyl ketone		
	Males	1	0.4 (0.1–4.0)
	Females	3	4.6 (0.9–23.2)
	Methylene chloride (males)	5	3.4 (0.9–13.2)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Lundberg and Milatou-Smith, 1998	Male Swedish paint-industry workers, ever employed		
	Incidence	4	3.2 (0.9–8.3)
Berlin et al., 1995	Swedish workers occupationally exposed to solvents	3	2.0 (0.4–5.7)
Lynge et al., 1995	Printing-industry workers in Denmark		
	Bookbinders, ever employed	1	1.27 (0.02–7.04)
	Typographer (printing establishment), ever employed	4	1.14 (0.31–2.93)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Factory workers, ever exposed	90	1.17 (0.95–1.45)[a]
	Mixed solvents, routine exposure	15	0.98 (0.55–1.61)
	Routine or intermittent exposure		
	<1 year of exposure	3	0.34 (0.10–1.14)
	1–4 years of exposure	13	0.63 (0.32–1.25)
	≥5 years of exposure	34	0.80 (0.46–1.38)
	Painter, employed >1 year	4	1.70 (0.46–4.35)
Steenland and Palu, 1999	US painters-union members		
	Painters	64	0.97 (0.75–1.24)
	20-year membership	54	1.01 (0.76–1.32)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Lundberg and Milatou-Smith, 1998	Male Swedish paint-industry workers, ever employed		
	Mortality	4	3.8 (1.0–9.7)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Any solvent		
	Males	19	1.3 (0.4–3.8)
	Females	5	1.9 (0.4–8.2)
Fu et al., 1996	Shoe-manufacturing workers		
	English cohort	7	0.99 (0.40–2.05)
	Probable solvent exposure	3	1.15 (0.24–3.36)
	High solvent exposure	1	5.26 (0.13–29.30)
	Florence cohort	3	3.70 (0.76–10.80)
	Probable solvent exposure	1	2.17 (0.05–12.10)
	High solvent exposure	1	2.44 (0.06–13.60)
Case–Control Studies			
Demers et al., 1993	Residents of four US states		
	Painters	31	2.1 (1.2–3.6)
	Employed <10 years	15	1.4 (0.6–2.8)
	Employed ≥10 years	16	4.1 (1.8–10.4)
	Printing machine operators	4	0.6 (0.1–2.0)
Eriksson and Karlsson, 1992	Residents of northern Sweden		
	Organic solvents (occupational), ever used	21	0.50 (0.30–0.80)[b]
	Duration of exposure (occupational)		
	≤5 years	NA	0.37 (0.09–1.48)[b]
	6–20 years	NA	0.59 (0.28–1.25)[b]
	≥21 years	NA	0.37 (0.26–0.74)[b]
	Organic solvents (leisure use), ever used	43	1.22 (0.80–1.89)[b]
Morris et al., 1986	Residents of four US states		
	Ever exposed to:		
	Aldehydes or ketones	7	1.1 (0.4–3.6)
	Aromatic hydrocarbons	16	0.8 (0.5–1.4)
	Chlorinated hydrocarbons	70	1.0 (0.7–1.4)
	Paints or solvents	39	1.8 (1.2–2.7)

NOTE: NA = not available.
[a]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.
[b]90% CI reported.

ADULT LEUKEMIA

With the introduction of the eighth and ninth revisions of the ICD codes and an increased ability to identify subtypes of leukemia, epidemiologists could more easily identify specific hematopoietic cancers in their studies. However, in most of the studies reviewed, especially those conducted early, it was not possible to identify specific subtypes of adult leukemia. Furthermore, in the small cohort studies, there were often insufficient cases of any particular type of leukemia, so all subtypes were combined in the analyses to improve statistical power. In contrast with the literature on insecticide exposure, there were enough studies on the specific subtypes of leukemia to present findings according to the following five groups: adult leukemia

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broadly, acute leukemia, chronic leukemia, lymphatic leukemia, and hairy cell leukemia. The committee acknowledges that the literature on adult leukemia could be divided by specific cell type but believes that there were too few studies to support valid conclusions on each specific type of leukemia. The committee therefore determined that there were enough high quality studies to support conclusions regarding the broad category of adult leukemia and acute leukemia only, which includes acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL). The decision to group leukemia types by onset (acute vs chronic) rather than by cell type was based on the available literature. The studies on acute leukemia, including AML and ALL, appeared to share more risk factors and findings than the more limited literature on chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL). Thus, the literature directed the committee to draw conclusions of association that encompassed both subtypes of acute leukemia.

Description of Case–Control Studies

The characteristics of the case–control studies considered by the committee in drawing its conclusions of association are described below in Table 6.39. All but one case–control study (Aschengrau et al., 1993) included interviews with study subjects concerning occupational history. Several questionnaires also included queries about specific chemical exposures, including benzene, trichloroethylene, and tetrachloroethylene (Albin et al., 2000; Bernard et al., 1984; Clavel et al., 1996; Nordström et al., 1998; Richardson et al., 1992; Staines and Cartwright, 1993). In many studies, experts reviewed questionnaire responses and attributed exposures unaware of case or control status (Albin et al., 2000; Ciccone et al., 1993; Clavel et al., 1996, 1998; Costantini et al., 2001; Lazarov et al., 2000; Malone et al., 1989; Richardson et al., 1992). Another study used a job—exposure matrix (Clavel et al., 1998) to determine exposures. However, in some studies, self-reported exposures were used as the metric (Bernard et al., 1984; Clavel et al., 1995; Flodin et al., 1981; Mele et al., 1994; Nordström et al., 1998; Staines and Cartwright, 1993). Unlike most occupational studies of leukemia, the study by Aschengrau and colleagues (1993) assessed exposure to tetrachloroethylene on the basis of estimated concentrations in public drinking water in five towns of Cape Cod, Massachusetts. Case–control studies of leukemia and exposure to organic solvents that had reasonably good assessments of exposure and enough exposed cases include those by Albin and colleagues (2000), Clavel and colleagues (1996), Lazarov and colleagues (2000), Malone and colleagues (1989), and Richardson and colleagues (1992).

Epidemiologic Studies of Exposure to Organic Solvents and Adult Leukemia

Several large cohort studies provided evidence for evaluating the association between exposure to benzene and adult leukemia. The principal cohort studies included several occupational populations with estimated levels of exposure, including the Pliofilm workers (Crump, 1994; Rinsky et al., 1981, 1987), Chinese factory workers (Hayes et al., 1997; Yin et al., 1996a,b), US chemical workers (Bond et al., 1986; Ireland et al., 1997; Wong, 1987a,b), US and British petroleum-distribution and oil-refinery workers (Rushton and Alderson, 1981; Wong et al., 1993), and, in nested case–control studies, petroleum-distribution workers in Canada (Schnatter et al., 1996a,b) and the UK (Rushton and Romaniuk, 1997).

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TABLE 6.39 Description of Case–Control Studies of Leukemia and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Viadana and Bross, 1972	White cases from the Tri-State Leukemia Survey, covering New York (New York City excluded), Baltimore, and Minnesota in 1959–1962; controls randomly selected from the same geographic areas	1345 leukemia	1,237	Painting work Printing work	In-person interviews (direct or proxy) to assess occupational history (job titles)	OR	Age
Flodin et al., 1981	Deceased cases, identified through the records of the Linkoping University Hospital (Sweden) and parish registers, in 1972–1978; controls selected from parish registers, matched for age and sex	42 AML	244	Solvents	Mailed questionnaire to next of kin to assess occupational exposures (self-reports)	Unadjusted OR	None
Bernard et al., 1984	Cases identified through registries and clinician reporting among residents of the Yorkshire Health Region, UK, with diagnosis in 1979–1981 and hematologic confirmation; controls selected from hospital inpatients, matched for age, sex, and geographic area	79 lymphoid leukemia	79	Benzene Solvents	In-person interview to assess occupational history (job titles) and details of solvent and chemical contacts (self-reports)	Logistic regression	Sex, age
Malone et al., 1989	Cases, age less than 80 years, diagnosed in four US SEER study areas in 1977–1981; controls selected through RDD or area sampling, depending on the study area, and matched for sex, race, and age Participation rates: 82.5% of cases, 83% of controls	427 CLL	1683	Dry-cleaning industry work Aromatic hydrocarbons Paints	Interview (in-person or telephone) with standardized questionnaire to assess lifetime occupational and leisure exposure history (self-reports)	Logistic regression	Age, sex, race, education level, area of residence
Richardson et al., 1992	Cases, age 30 years or over, identified through hospital hematology departments in Paris and Creteil, France, in 1984–1988; hospital controls selected from other departments, matched for sex, age, ethnicity, and usual residence	185 acute leukemia	513	Benzene Solvents Other hydrocarbon solvents Halogenated solvents Oxygenated solvents	Interview with standardized questionnaire to assess lifetime occupational and leisure exposure history (self-reports) with solvent- exposure probability and level determined by industrial hygienist review	Conditional logistic regression	Matching variables, prior history of radio-therapy or chemotherapy

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Aschengrau et al., 1993	Cases reported to the Massachusetts Cancer Registry, diagnosed in 1983–1986 among residents of five upper Cape Cod towns; living controls were selected from the records of the HCFA and through RDD; deceased controls identified by the state Department of Vital Statistics and Research files Response rates: 79.5% of cases, 75.9% of HCFA controls, 73.9% of RDD controls, 78.8% of next of kin of deceased controls	34 leukemia	737	Tetrachloroethylene	Relative delivered dose estimated in model accounting for location and years of residence, water flow, pipe characteristics	Logistic regression	Sex, age at diagnosis, vital status, educational level, occupational exposure to solvents, specific cancer risk factors
Ciccone et al., 1993	Cases, age 15–74 years, treated in the Main Hospital of Torino, Italy, newly diagnosed in 1989–1990; hospital controls selected in the same interval, matched for sex, age, and area of residence; population controls randomly selected from residents of Torino, matched on above Response rates: 91% of cases, 99% of hospital controls, 82% of population controls	50 AML 17 CML	246	Benzene	Interview with standardized questionnaire to assess lifetime occupational history (job titles) with exposure to solvents determined by industrial hygienist	Logistic regression	Age, area of residence and of birth, smoking
Staines and Cartwright, 1993	Cases from the Yorkshire and Trent (UK) Regional Health Authority areas, identified through Leukemia Research Fund data collection or hematologist participation in 1985–1990 with histologic confirmation; hospital controls matched for sex, age, and hospital	50 HCL	95	Benzene Solvents Organic chemicals	In-person interview with structured questionnaire to assess occupational history and exposure to chemicals (self-reports)	Conditional logistic regression	Matching variables
Mele et al., 1994	Cases, age 15 years or over, identified by hematology departments in three Italian cities in 1986–1990; outpatients without hematologic disorders selected as controls	252 AML 100 ALL 156 CML	1,161	Painting work Shoemakers	In-hospital interview to assess lifetime behavioral and occupational exposure histories (job titles; self-reports)	Logistic regression	Age, sex, education, residence outside study town, other occupations

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Clavel et al., 1995	Cases diagnosed in 18 French hospitals in 1980–1990; hospital controls selected from admission records during same interval, matched on sex, date of birth, date of admission, and residence (see also Clavel et al., 1996, 1998)	291 HCL 229 men 62 women	541 425 men 116 women	Solvents	Mailed questionnaire to assess lifetime occupational history (job titles) with supplementary telephone interview on exposure to solvents (self-reports)	Conditional logistic regression	Matching variables
Clavel et al., 1996	Male cases diagnosed in 18 French hospitals in 1980–1990; hospital controls selected from admission records during same interval, matched on sex, date of birth, date of admission, and residence (see also Clavel et al., 1995, 1998)	226 HCL	425	Benzene Painters	Mailed questionnaire to assess lifetime occupational history (job titles) with supplementary telephone interview on exposure to solvents (self-reports) and use of job–exposure matrix	Conditional logistic regression	Matching variables, smoking, farm work
Clavel et al., 1998	Male cases diagnosed in 18 French hospitals in 1980–1990; hospital controls selected from admission records during same interval, matched on sex, date of birth, date of admission, and residence (see also Clavel et al., 1995, 1996)	226 HCL	425	Organic solvents Launderers and dry cleaners Painters Printers Spray painters	Mailed questionnaire to assess lifetime occupational history (job titles) with supplementary telephone interview on exposure to solvents (self-reports) and use of job–exposure matrix	Conditional logistic regression	Matching variables, smoking, farm work
Nordström et al., 1998	Male cases reported to the Swedish Cancer Registry in 1987–1992; controls selected from the National Population Registry, matched for age and county	111 HCL	400	Trichloroethylene Acetone White spirit Solvents Paint	Mailed questionnaire (with supplemental telephone followup) to assess lifetime occupational history (job titles) and exposure to solvents (self-reports)	Logistic regression	Age

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Albin et al., 2000	Consecutively diagnosed cases, age at least 20 years, at the Department of Clinical Genetics in Lund, Sweden, in 1976–1993 with hematologic confirmation; population-based controls selected through Statistics Sweden, matched for sex, year of birth, and county Participation rates: 90% of cases, 72% of controls	333 AML	351	Benzene Chlorinated solvents Organic solvents	Telephone interview (direct or proxy) obtained lifetime occupational and leisure exposure histories (self-reports); team of occupational hygienists performed exposure assessment	Logistic regression	Age, sex
Lazarov et al., 2000	Consecutive white cases, age 18 years or over, identified through hematology departments in Novi Sad, Yugoslavia in 1986–1990, and London, England, in 1988–1994; controls selected from hospital inpatients, matched for hospital, admission year, sex, and age	98 AML	196	Solvents Painting work Paints Oils Machinery Mechanics and fitters	In-person interview with questionnaire to assess occupational and exposure histories (self-reports)	Unadjusted OR, conditional logistic regression	Medication history, smoking status
Costantini et al., 2001	Cases, age 20–74 years, identified through periodic hospital survey and diagnosed in 12 regions of Italy in 1991–1993 with hematologic confirmation; controls randomly selected from municipal demographic files and the National Health Services files, matched for age and sex Response rates: 88% of cases, 81% of controls	652 leukemia	1,779	Launderers, dry cleaners, pressers Painting work	In-person interview (direct or proxy) with standardized and job-specific questionnaires to assess lifetime occupational history (job titles) and exposure to solvents (self-reports); probability of exposure further determined by industrial hygienist	Mantel-Haenszel OR	Age, sex

NOTE: ALL = acute lymphatic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphatic leukemia; CML = chronic myeloid leukemia; HCL = hairy cell leukemia; SEER = Surveillance, Epidemiology, and End Results; RDD = random-digit dialing; HCFA = Health Care Financing Administration.

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In the Pliofilm workers study (Crump, 1994; Rinsky et al., 1981, 1987), subjects included workers exposed to benzene for at least 1 day from 1940 to 1950. In the last followup study, there were 14 deaths from leukemia, resulting in an SMR of 2.9 (95% CI = 1.61–4.95). The relative risk of leukemia was found to increase with cumulative exposure, regardless of the methods used to estimate levels of exposure. In the study by Crump (1994), the RR was 1.2 (95% CI = 0.26–3.64) for exposure at 0–45 ppm per year and 3.1 for exposure at 400–1,000 ppm per year (95% CI = 0.37–11.11); in the Rinsky and colleagues' study (1987), the RR was 1.09 (95% CI = 0.12–3.94) for 0.001–40 ppm per year and 3.22 (95% CI = 0.36–11.65) for 40–200 ppm per year.

Yin and colleagues (1996a) investigated the relationship between leukemia and exposure to benzene among Chinese workers and reported increased leukemia mortality (RR = 2.3, 95% CI = 1.1–5.0) and incidence (RR = 2.6, 95% CI = 1.3–5.7). Hayes and colleagues (1997) evaluated the exposure–response relationships and did not find clear dose–response relationships, but they did find that the relative risks generally increased by year of hire, average exposure (ppm), duration of employment (years), and cumulative exposure (ppm-years).

Evidence of an association between exposure to benzene and leukemia was also provided by several other cohort studies, including studies of US chemical workers and petroleum-distribution workers. The studies tended to be small and lacked the statistical power to detect a small to moderate association. Specifically, findings from the US chemical-worker studies (Bond et al., 1986; Ireland et al., 1997; Wong, 1987a,b) showed increased risks but no clear dose–response relationships. Associations were found in the UK study of oil-refinery workers (SMR = 2.33, 95% CI = 0.98–5.56) (Rushton and Alderson, 1981) and the study of petroleum-marketing and -distribution workers (SMR = 1.35, 95% CI = 0.14–12.8 for at least 45 ppm per year), but no clear dose–response pattern emerged (Rushton and Romaniuk, 1997). In the study of Canadian petroleum-distribution workers (Schnatter et al., 1996a), no associations were found.

Associations between exposure to trichloroethylene and leukemia were not found in several cohort studies that had relatively accurate information on occupational exposures. They included studies of biologically monitored workers (Hansen et al., 2001), workers at a uranium-processing plant (Ritz, 1999), and aircraft and aerospace maintenance and manufacturing workers (Blair et al., 1998; Boice et al., 1999; Morgan et al., 1998). The studies were generally of high quality with sufficient statistical power to detect relative risks of leukemia.

Investigations of most other specific organic solvents were restricted to single studies, and estimates of relative risk were usually based on small numbers of exposed cases. As a result, in most studies, no associations with leukemia were reported (Boice et al., 1999; Dosemeci et al., 1991). However, in one study of Swedish rotogravure-plant workers (Svensson et al., 1990) exposed to toluene, an increased risk of leukemia was observed (SMR = 1.67, 95% CI = 0.34–4.88). The risk was higher in those exposed for 5 years or more and with at least a 10-year latency (SMR = 2.54, 95% CI = 0.52–7.42).

Occupations in which large quantities of organic solvents were used have been studied to identify health risks and instigate interventions to reduce exposure. In several studies reviewed by the committee, increased risks of leukemia were observed among painters (Costantini et al., 2001: OR = 1.7, 95% CI = 0.8–3.8; Lundberg and Milatou-Smith, 1998: SIR = 1.5, 95% CI = 0.3–4.3; Viadana and Bross, 1972: RR = 2.82), car mechanics (Hunting et al., 1995: SMR = 9.26, 95% CI = 1.12–33.43), shoe-manufacturing workers (Fu et al., 1996: SMR = 2.80, 95% CI = 0.76–7.16; Paci et al., 1989: SMR = 4.95, 95% CI = 1.82–10.79), employees at a naval nuclear shipyard (Stern et al., 1986: OR = 2.32, 95% CI = 0.85–6.29), workers exposed to solvents

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occupationally (Berlin et al., 1995: SIR = 2.1, 95% CI = 0.8–4.6), and leather or tannery workers (Costantini et al., 1989: SMR = 1.64, 95% CI = 0.53–3.82). Studies in which associations were not found (Anttila et al., 1998; Boice et al., 1999; Garabrant et al., 1988; Matanoski et al., 1986; Steenland and Palu, 1999; Walker et al., 1993; Wolf et al., 1981; Wong et al., 1993) generally had small numbers of exposed cases. Two studies (Anttila et al., 1995; Fu et al., 1996) provided evidence of a dose–response relationship with increasing relative risks as exposure increased.

Summary and Conclusion

IARC and the US Environmental Protection Agency (EPA) have determined that benzene is carcinogenic in humans on the basis of both animal and human studies (ATSDR, 1997a; IARC, 1987; NTP, 2001). That determination was based primarily on the findings on leukemia defined broadly. In addition, epidemiologic studies of occupations exposed to mixtures of solvents, including benzene have shown increased risks of developing cancer. Among those at risk are rubber workers, mechanics, and some groups of chemical workers, printers and paper-industry workers, and shoe and leather workers (IARC, 1987, 1989).

Based on its review of the literature on exposure to benzene, the committee found that the combination of consistently positive findings in the cohort of workers with known exposures to benzene and evidence of a dose–response relationship fulfilled the criteria for a conclusion of sufficient evidence of an association between exposure to benzene and adult leukemia. However, the committee decided that the evidence of an association between exposure to benzene and adult leukemia was not as strong as that for acute leukemia. Thus, it did not warrant a conclusion of causality. The findings, although mostly positive, are not as consistent and statistically precise as the findings on acute leukemia. Most likely, the positive studies on adult leukemia and exposure to benzene include cases of acute leukemia. However, they may also include cases of chronic leukemia, lymphatic leukemia, and hairy cell leukemia, for which the existence of associations is not as clear. On the basis of the studies reviewed, the committee believes that the evidence on exposure to benzene and adult leukemia, defined broadly, met the definition of sufficient evidence of an association but not sufficient evidence of a causal relationship.

The committee concludes, from its assessment of the epidemiologic literature, that there is sufficient evidence of an association between chronic exposure to benzene and adult leukemia.

For exposure to other solvents, such as trichloroethylene and toluene, the overall paucity of studies and the lack of consistently positive findings limits the evidence that the committee had to review.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to specific organic solvents under review, other than benzene, and adult leukemia.

In contrast, the findings for unspecified mixtures of organic solvents and adult leukemia showed increased relative risks, including two studies that provided evidence for a dose–response relationship with increasing levels of exposure. Table 6.40 identifies the key studies reviewed by the committee on adult leukemia. Unless indicated in the table, the study populations include both men and women.

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The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of association between chronic exposure to unspecified mixtures of organic solvents and adult leukemia.

TABLE 6.40 Selected Epidemiologic Studies—Adult Leukemia and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Studies—Mortality			
Crump, 1994	Male US Pliofilm workers	14	2.9 (1.61–4.95)[a]
	Cumulative exposure		
	0–45 ppm-years	3	1.2 (0.26–3.64)[a]
	45–400 ppm-years	4	2.7 (0.73–6.83)[a]
	400–1,000 ppm-years	2	3.1 (0.37–11.11)[a]
	>1000 ppm-years	5	28.1 (9.00–64.83)[a]
Yin et al., 1996a	Chinese factory workers		
	Mortality, total	38	2.3 (1.1–5.0)
	Males	25	2.1 (1.0–5.3)
	Females	13	2.8 (0.8–17.6)
		42	
	Incidence, total		2.6 (1.3–5.7)
Hayes et al., 1997	Chinese factory workers		
	All exposed workers	38	2.5 (1.2–5.1)
	Exposed workers, year of hire		
	<1972	25	2.4
	≥1972	13	3.4
	Exposed workers, average ppm		
	<10	15	2.0 (0.9–4.5)
	10–24	13	3.7 (1.6–8.7)
	≥25	10	2.3 (0.9–5.7)
			p trend = 0.02
	Exposed workers, duration		
	<5 years	14	4.0 (1.7–9.6)
	5–9 years	11	3.1 (1.3–7.5)
	≥10 years	13	1.5 (0.6–3.6)
			p trend = 0.98
	Exposed workers, cumulative exposure		
	<40 ppm-years	11	1.9 (0.8–4.7)
	40–99 ppm-years	8	3.1 (1.2–8.0)
	≥100 ppm-years	19	2.7 (1.2–6.0)
			p trend = 0.04
Ireland et al., 1997	Male US chemical-plant workers		
	<12 ppm-months	2	2.5 (0.3–8.9)
	12–72 ppm-months	0	0.0 (0.0–5.4)
	≥72 ppm-months	3	4.6 (0.9–13.4)
Rushton and Romaniuk, 1997	Male UK petroleum marketing and distribution workers		
	Cumulative exposure		
	<0.45 ppm-years	22	1.00
	0.45–4.49 ppm-years	47	1.42 (0.77–2.61)
	4.5–44.9 ppm-years	20	2.48 (0.73–3.00)
	≥45 ppm-years	1	1.35 (0.14–12.8)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Schnatter et al., 1996a	Male Canadian petroleum distribution workers		
	By median, 75th, and 90th percentiles		
	0.0–0.49 ppm-years	10	1.00
	0.50–7.99 ppm-years	1	0.22 (0.0–1.82)
	8.0–19.99 ppm-years	1	0.42 (0.01–3.95)
	20.0–219.8 ppm-years	2	0.96 (0.09–6.81)
	Exposure by regulatory standards		
	0.00–0.45 ppm-years	10	1.00[b]
	>0.45–4.5 ppm-years	1	0.43 (0.0–4.05)
	4.5–45 ppm-years	1	0.16 (0.0–4.55)
	≥45 ppm-years	2	1.47 (0.16–13.1)
Rinsky et al., 1987	Male US Pliofilm workers		
	Ever exposed	9	3.37 (1.54–6.41)
	0.001–40 ppm-years	2	1.09 (0.12–3.94)
	40–200 ppm-years	2	3.22 (0.36–11.65)
	200–400 ppm-years	2	11.86 (1.33–42.85)
	>400 ppm-years	3	66.37 (13.34–193.9)
Wong, 1987a,b	Male chemical manufacturing workers		
	Entire cohort	7	0.75 (0.30–1.54)
	Continuously exposed	6	1.35 (0.49–2.95)
	Cumulative exposure		
	<180 ppm-months	2	0.97 (0.12–3.49)
	180–719 ppm-months	1	0.78 (0.20–4.34)
	≥720 ppm-months	3	2.76 (0.57–8.06)
Bond et al., 1986	Male chemical workers, ever exposed		
	Cohort less those exposed to arsenic, asbestos, or high levels of vinyl chloride	3	1.62 (0.33–4.61)
Rushton and Alderson, 1981	Male employees in eight UK oil refineries, ever exposed	NA	2.33 (0.98–5.56)
Trichloroethylene			
Cohort Study—Incidence			
Hansen et al., 2001	Biologically monitored Danish workers		
	Males	5	1.9 (0.6–4.4)
	Females	1	3.1 (0.04–18.0)
Cohort Studies—Mortality			
Ritz, 1999	White male employees at a uranium-processing plant in Ohio	12	1.09 (0.56–1.91)
Boice et al., 1999	Aircraft-manufacturing workers in California, ever exposed	2	1.05 (0.54–1.84)
Blair et al., 1998	Aircraft-maintenance workers in Utah		
	Combined early and recent followup cohort	16	0.6 (0.3–1.2)
	Men (cumulative exposure)		
	No exposure	9	1.0 (0.4–2.9)
	<5 unit-years	7	1.0 (0.3–3.2)
	5–25 unit-years	0	—
	>25 unit-years	7	1.2 (0.4–3.6)
Morgan et al., 1998	Aerospace workers in Arizona, ever exposed	10	1.05 (0.50–1.93)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Other Specific Organic Solvents			
Cohort Study—Incidence			
Svensson et al., 1990	Male rotogravure workers in Sweden—toluene		
	All exposed	3	1.67 (0.34–4.88)
	≥5 years of exposure and >10-year latency	3	2.54 (0.52–7.42)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Ever exposed—tetrachloroethylene	5	1.09 (0.35–2.55)
Dosemeci et al., 1991	Male workers exposed to phenol		
	No exposure	7	0.9
	All exposed	14	0.9 (0.5–1.4)
	High exposure	1	0.8
	Medium exposure	5	0.7
	Low exposure	8	1.0
Case–Control Studies			
Costantini et al., 2001	Residents of 12 areas of Italy		
	Launderers, dry cleaners, pressers, ever employed	2	3.3 (0.3–32.4)
Aschengrau et al., 1993	Residents of Cape Code, MA—tetrachloroethylene		
	Exposure history		
	Any	7	1.77 (0.63–4.33)
	Low	5	1.38 (0.40–3.78)
	High	2	5.95 (0.58–31.72)
Unspecified Mixtures of Organic Solvents			
Cohort Studies—Incidence			
Anttila et al., 1998	Finnish workers monitored for exposure to solvents		
	Aromatic hydrocarbons, all years	1	0.30 (0.01–1.67)
Lundberg and Milatou-Smith, 1998	Swedish paint-industry workers		
	Incidence, male workers, ≥5 years	3	1.5 (0.3–4.3)
Berlin et al., 1995	Swedish workers occupationally exposed to solvents		
	Incidence	6	2.1 (0.8–4.6)
Anttila et al., 1995	Finnish workers exposed to halogenated hydrocarbons		
	Ever exposed, male and female for the entire measurement period	5	1.08 (0.35–2.53)
	Mean personal level		
	<100 µmol/L	1	0.39 (0.01–2.19)
	100+ µmol/L	4	2.65 (0.72–6.78)
Cohort Studies—Mortality			
Boice et al., 1999	Aircraft-manufacturing workers in California		
	Mixed solvents, ever exposed	28	1.02 (0.68–1.48)
Steenland and Palu, 1999	Painter-union members		
	Painters (all members)	138	0.92 (0.78–1.11)
	Painters (20 years since first union membership)	111	1.11 (0.74–1.08)
Lundberg and Milatou-Smith, 1998	Swedish paint-industry workers		
	Mortality, male workers, ≥5 years	2	1.2 (0.2–4.3)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Fu et al., 1996	Shoe-manufacturing workers		
	English cohort	16	0.89 (0.51–1.45)
	Probable solvent	4	0.68 (0.19–1.75)
	High solvent	0	—
	Florence cohort	8	2.14 (0.92–4.21)
	Probable solvent	4	2.52 (0.69–6.44)
	High solvent	4	2.80 (0.76–7.16)
Hunting et al., 1995	Male vehicle mechanics in the District of Columbia		
	Solvents or fuels, high exposure	2	9.26 (1.12–33.43)
Berlin et al., 1995	Swedish workers occupationally exposed to solvents		
	Mortality	4	2.3 (0.6–5.8)
Walker et al., 1993	Shoe-manufacturing workers, employed >1 month	15	1.11 (0.63–1.85)
Wong et al., 1993	Gasoline distribution workers in the United States		
	Land-based terminal cohort	27	0.89 (0.59–1.29)
	Marine-based terminal cohort	16	0.70 (0.42–1.09)
Costantini et al., 1989	Male tannery workers in Tuscany, employed >6 months	5	1.64 (0.53–3.82)
Paci et al., 1989	Shoe factory workers in Italy		
	Total years of exposure (males)	6	4.95 (1.82–10.79)[a]
Garabrant et al., 1988	Aircraft manufacturing workers in California		
	Employed >4 years	16	0.82 (0.47–1.34)
Matanoski et al., 1986	Painters and allied tradesmen union members	44	0.93 (0.68–1.25)[b]
Stern et al., 1986	Male employees at a naval nuclear shipyard		
	Ever worked in job with solvent exposure	NA	2.32 (0.85–6.29)
	8.59 years in a solvent job	NA	1.82 (0.93–3.58)
Wolf et al., 1981	Workers in the US rubber industry		
	High solvent	8	0.8 ($p = 0.64$)
	Medium solvent	38	1.1 ($p = 0.79$)
	Low solvent	23	0.6 ($p = 0.05$)
Alderson and Rattan, 1980	Male chemical-plant workers		
	Methyl ethyl ketone plant production workers	1	2.86 (0.07–15.91)[a]
Chiazze et al., 1980	Male spray painters at automobile-assembly plants	2	1.13 (0.14–4.08)[b]
Case–Control Studies			
Costantini et al., 2001	Residents of 12 areas of Italy		
	Painters, ever employed	10	1.7 (0.8–3.8)
Viadana and Bross, 1972	Residents of New York, Baltimore, and Minnesota (Tri-State Leukemia Survey)		
	Painters, white males		
	15–44 years	4	2.20
	45–64 years	12	3.29
	65–48 years	15	2.90

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Printers, white males		
	15–44 years	2	8.50
	45–64 years	4	1.40
	65–48 years	11	1.00

NOTE: NA = not available.
[a]95% CI were calculated by the committee with standard methods from the observed and expected numbers presented in the original papers.
[b]Estimated risks and 95% CI were calculated by the committee with standard methods from the observed and expected numbers presented in the original papers.

Epidemiologic Studies of Exposure to Organic Solvents and Acute Leukemia

Virtually all studies of exposure to benzene and acute leukemia (specifically AML or acute nonlymphocytic leukemia [ANLL], and ALL) showed positive associations (Albin et al., 2000; Ciccone et al., 1993; Crump, 1994; Ireland et al., 1997; Richardson et al., 1992; Rushton and Romaniuk, 1996; Wong, 1995; Yin et al., 1996a,b). In several cohort and case–control studies, the risks of acute leukemia were found to increase as the level or duration of exposure to benzene increased (Ireland et al., 1997; Richardson et al., 1992; Rushton and Romaniuk, 1996; Wong, 1995).

Increases in incidence of and mortality from AML were reported in the cohort studies of Chinese factory workers (SMR = 3.1, 95% CI = 1.2–10.7) (Yin et al., 1996a,b) and Pliofilm workers in Ohio (SMR = 5.03, 95% CI = 1.84–10.97) (Wong, 1995) respectively. Increased risks of AML were also reported in the cohort of petroleum-distribution workers in the UK (Rushton and Romaniuk (1996) and in a case–control study in Sweden by Albin and colleagues (2000) (OR = 1.5, 95% CI = 0.89–2.6 for all exposure levels). In a case–control study in France, Richardson and colleagues (1992) found an increased odds ratio among those with "medium/high" exposure to benzene (OR = 2.8, 95% CI = 1.3–5.9) when other occupational exposures were adjusted for. Increased risk of ANLL (RR = 1.4, 95% CI = 0.4–3.42) was reported from the cohort study of Monsanto chemical workers (Ireland et al., 1997). Yin and colleagues (1996a,b) found increased ALL risk among benzene-exposed workers, although the CIs were quite broad (SIR = 2.8, 95% CI = 0.5–54.5). Weak positive associations were observed in a low-powered case–control study in which exposure to solvents was assessed by industrial hygienists (Ciccone et al., 1993).

A number of case–control studies showed mostly positive associations between acute leukemia and exposure to unspecified mixtures of organic solvents (Albin et al., 2000; Flodin et al., 1981; Lazarov et al., 2000; Mele et al., 1994; Richardson et al., 1992). To increase the accuracy of exposure and to reduce recall bias, industrial hygienists, unaware of the case status of subjects, attributed exposure on the basis of job descriptions (Albin et al., 2000; Lazarov et al., 2000; and Richardson et al., 1992). In a case–control study by Albin and colleagues (2000), the OR for AML for all levels of exposure to organic solvents was 1.6 (95% CI = 1.1–2.4) and 2.3 (95% CI = 1.0–5.0) for moderate to high levels of exposure. For exposure to solvents in general, Lazarov and colleagues (2000) also showed an increased risk of AML (OR = 2.52, 95% CI = 1.45–4.39); the risk increased to 3.86 (95% CI = 1.83–8.14) for "probable exposure" to solvents. In the case–control study by Flodin and colleagues (1981), the risk of AML increased to 6.3 (95% CI = 2.6–15.3). A study of people ever employed as painters or shoemakers showed increased relative risks of both AML and ALL: for painters, the OR was 3.2 (95% CI = 0.5–20.8)

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for AML and 4.7 (95% CI = 0.6–34.2) for ALL; for shoemakers, the OR was 2.4 (95% CI = 0.9–6.9) for AML and 1.3 (95% CI = 0.2–10.2) for ALL.

Summary and Conclusion

On the basis of the consistently high relative risks in studies in which the exposure to benzene is well known, the committee decided that the evidence meets the requirement for a conclusion of causality between chronic exposure to benzene and acute leukemia. Furthermore, given the strong positive associations in the cohort studies of highly exposed subjects, it is likely that confounding and selection bias do not account for the findings. Experimental evidence supports a biologic mechanism that strengthens the conclusion. The details of that experimental evidence are provided in Chapter 4 and discussed below.

The metabolism of benzene, which occurs in the liver and to a smaller extent in the bone marrow, plays an important role in its toxicity. Benzene is metabolized to benzene oxide, an epoxide, through an oxidation reaction catalyzed primarily by cytochrome P450 2E1. Benzene oxide can be metabolized to various compounds, including *o*-benzoquinone and *p*-benzoquinone, which are thought to be the two main metabolites that mediate the toxicity of benzene. Data on laboratory animals show that benzene affects the bone marrow in a dose-dependent manner, causing anemia, leukopenia, and thrombocytopenia; continued exposure causes aplasia and pancytopenia (Bruckner and Warren, 2001). Benzene also has carcinogenic properties. In experimental animals, increases in incidence of malignant lymphoma and some solid tumors have been seen after exposure to high doses of benzene.

The committee concludes, from its assessment of the epidemiologic and experimental literature, that there is sufficient evidence of a causal relationship between chronic exposure to benzene and acute leukemia.

For exposure to unspecified mixtures of organic solvents, the studies were virtually all positive, including several that were statistical strong. One study provided evidence of an exposure–response relationship in terms of both increasing levels and increasing duration of exposure. Table 6.41 identifies all the studies reviewed by the committee. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is sufficient evidence of an association between chronic exposure to unspecified mixtures of organic solvents and acute leukemia.

TABLE 6.41 Selected Epidemiologic Studies—Acute Leukemia and Exposure to Organic Solvents

Reference	Study Population and Cancer Type	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Studies—Mortality			
Ireland et al., 1997	Male Monsanto Company production workers in Sauget, Illinois—ANLL		
	<12 ppm-months	1	3.7 (0.1–20.6)
	12–72 ppm-months	0	0.0 (0.0–44.1)
	>72 ppm-months	1	4.5 (0.1–25.3)
	Ever exposed	4	1.4 (0.4–3.42)[a]

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Reference	Study Population and Cancer Type	Exposed Cases	Estimated Relative Risk (95% CI)
Rushton and Romaniuk, 1996	Male petroleum-distribution workers in the UK—AML (myeloid and monocytic)		
	<0.45 ppm-years	7	1
	0.45–4.49 ppm-years	15	2.17 (0.77–6.09)
	4.5–44.9 ppm-years	9	2.82 (0.82–9.38)
	>45 ppm-years	—	—
Yin et al., 1996a,b	Chinese factory workers, ever exposed		
	Incidence of AML	23	3.1 (1.2–10.7)
	Incidence of ALL	5	2.8 (0.5–54.5)
Wong, 1995	Male Pliofilm workers in Ohio—AML (myeloid and monocytic)		
	<40 ppm-years	1	1.19 (0.03–6.63)
	40–200 ppm-years	0	0 (0–14.75)
	200–400 ppm-years	2	27.21 (3.29–98.24)
	>400 ppm-years	3	98.37 (20.28–287.65)
	Total	6	5.03 (1.84–10.97)
Crump, 1994	Male Pliofilm workers in Ohio—AML (myeloid and monocytic)		
	Total (two cases could not be identified as to type)	8–10	5.0–6.2
	0–45 ppm-years)	0–2	0.0–2.4
	45–400 ppm-years	1	2.0 (0.05–10.92)[b]
	400–1000 ppm-years	2	9.1 (1.10–32.82)[b]
	>1000 ppm-years	5	82.8 (27.00–194.50)[b]
Case–Control Studies			
Albin et al., 2000	Residents of Lund, Sweden—AML		
	All exposure levels	39	1.5 (0.89–2.6)
	Hobby—low levels	28	1.6 (0.89–3.1)
	Moderate–high levels	11	1.3 (0.52–3.1)
Ciccone et al., 1993	Residents in the Main Hospital of Torino, Italy—AML, CML, MDS; ever exposed	10	1.7 (0.6–5.5)
Richardson et al., 1992	Residents of Paris and Créteil, France—acute leukemia; occupationally exposed		
	All exposure levels	22	1.3 (0.8–2.3)
	High or medium exposure	15	2.8 (1.3–5.9)
Unspecified Mixtures of Organic Solvents			
Case–Control Studies			
Albin et al., 2000	Residents of Lund, Sweden—AML		
	Organic solvents, all exposure levels	88	1.6 (1.1–2.4)
	Low levels (hobby use)	70	1.5 (1.0–2.3)
	1–7 years-duration	10	0.72 (0.32–1.6)
	8–14 years-duration	18	1.5 (0.73–3.1)
	15–20 years-duration	42	2.1 (1.2–3.7)
	Moderate–high levels	18	2.3 (1.0–5.0)
	Moderate for 1–20 years	9	1.6 (0.57–4.3)
	High for 1–20 years	9	3.9 (1.0–15)
	Chlorinated solvents	12	0.78 (0.36–1.7)

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Reference	Study Population and Cancer Type	Exposed Cases	Estimated Relative Risk (95% CI)
Lazarov et al., 2000	Residents of Novi Sad, Yugoslavia, and London, England—AML		
	Solvents (multivariate analysis)	53	2.52 (1.45–4.39)
	Possible exposure	24	2.28 (1.12–4.62)
	Probable exposures	29	3.86 (1.83–8.14)
	Painters and related workers	7	4.57 (1.29–16.14)
	Paints	23	1.28 (0.68–2.43)
	Oils	32	1.56 (0.87–2.81)
	Machinery mechanics and fitters	12	4.03 (1.44–11.23)
Mele et al., 1994	Residents of Italy		
	Painters, ever employed		
	AML	4	3.2 (0.5–20.8)
	ALL	4	4.7 (0.6–34.2)
	Shoemakers, ever employed	4	2.4 (0.9–6.9)
	AML	1	1.3 (0.2–10.2)
	ALL		
Richardson et al., 1992	Residents of Paris and Créteil, France—acute leukemia; ever exposed		
	Solvents, all exposure levels	71	1.1 (0.7–1.5)
	Other hydrocarbon solvents, all exposure levels	28	1.0 (0.6–1.6)
	High or medium exposure	11	0.9 (0.4–1.8)
	Halogenated solvents, all exposure levels	44	1.1 (0.7–1.6)
	High or medium exposure	23	1.0 (0.6–1.7)
	Oxygenated solvents, all exposure levels	42	1.5 (1.0–2.4)
	High or medium exposure	15	1.5 (0.7–2.7)
Flodin et al., 1981	Residents of Linköping, Sweden—AML		
	Solvents, ever exposed	11	6.3 (2.6–15.3)[b]

[a]RR and 95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.
[b]95% CI calculated by the committee with standard methods from the observed and expected numbers presented in the original study.

Epidemiologic Studies of Exposure to Organic Solvents and Chronic Leukemia

An association between exposure to benzene and risk of chronic leukemia was reported in several studies (Ireland et al., 1997: SMR = 2.3, 95% CI = 0.7–5.3; Rushton and Romaniuk, 1997: SMR = 1.22, 95% CI = 0.38–3.89 for 4.5–44.9 ppm-years; Yin et al., 1996a,b: SMR = 2.6, 95% CI = 0.7–16.9). No excess risks (OR = 1.1, 95% CI = 0.6–2.0) were observed for self-reported exposure to aromatic hydrocarbons (the class of solvents that includes benzene, toluene, and xylene) in a population-based case–control study of CLL (Malone et al., 1989). Except for one exposure level, the case–control study by Rushton and Romaniuk (1997) showed relative risks close to unity.

A case–control study of leukemia and preleukemia conducted in Italy found that shoemakers and painters were at high risk for CML (OR = 4.5, 95% CI = 1.6–13.0 for shoemakers; OR = 7.6, 95% CI = 1.5–39.8 for painters) (Mele et al., 1994). Positive associations between exposure to mixed solvents and CLL were found in a US study reporting previous exposures to paints (OR = 1.4, 95% CI = 0.8–2.2) and hobby painting (OR = 1.4, 95% CI = 0.9–

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2.0), but no increased risks were found (OR = 0.9) among those employed in the dry-cleaning industry (Malone et al., 1989).

The committee drew no conclusion on an association between exposure to benzene or unspecified mixtures of organic solvents and chronic leukemia. Table 6.42 identifies the studies reviewed by the committee on chronic leukemia. Unless indicated in the table, the study populations include both men and women.

TABLE 6.42 Selected Epidemiologic Studies—Chronic Leukemia and Exposure to Organic Solvents

Reference	Study Population and Cancer Type	Exposed Cases	Estimated Relative Risk (95 % CI)
Benzene			
Cohort Studies—Mortality			
Ireland et al., 1997	Male Monsanto plant workers in Sauget, IL		
	Production workers exposed to benzene (all leukemias)	5	2.3 (0.7–5.3)
	CLL (exposure to benzene category)		
	<12 ppm-months	1	5.9 (0.1–32.6)
	12–72 ppm-months	0	0.0 (0.0–24.7)
	>72 ppm-months	1	6.7 (0.2–37.7)
Rushton and Romaniuk, 1997	Male UK petroleum marketing and distribution workers		
	CLL (exposure to benzene)		
	<0.45 ppm-years	8	1
	0.45–4.49 ppm-years	16	1.07 (0.40–2.86)
	4.5–44.9 ppm-years	7	1.22 (0.38–3.89)
	≥45 ppm-years	0	0
	CML (exposure to benzene)		
	<0.45–4.49 ppm-years	9	1
	4.5–44.9 ppm-years	2	0.76 (0.14–4.06)
	≥45 ppm-years	0	—
Yin et al., 1996a,b	Chinese factory workers—CML		
	Any exposure	9	2.6 (0.7–16.9)
Case–Control Study			
Malone et al., 1989	US residents of four areas—CLL		
	Aromatic hydrocarbons, any exposure	26	1.1 (0.6–2.0)
Unspecified Mixtures of Organic Solvents			
Case–Control Studies			
Mele et al., 1994	Residents of Italy		
	Painters, ever employed—CML	5	7.6 (1.5–39.8)
	Shoemakers, ever employed—CML	6	4.5 (1.6–13.0)
Malone et al., 1989	US residents of four areas—CLL		
	Paints, ever exposed	26	1.4 (0.8–2.2)
	Dry-cleaning industry, ever employed	14	0.9 (0.4–1.8)
	Hobby painting, ever exposed	48	1.4 (0.9–2.0)

Epidemiologic Studies on Exposure to Organic Solvents and Lymphatic Leukemia

Several studies of lymphatic leukemia examined associations with exposure to benzene. Positive associations between lymphatic leukemia and exposure to benzene were observed in several studies (Bernard et al., 1984; Wilcosky et al., 1984), but there was considerable variability in the estimates.

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Wilcosky found increased risk estimates associated with almost all exposures, including ethyl acetate (OR = 5.3, $p < 0.05$) and acetone (OR = 6.8, $p < 0.01$); this study was a large-scale investigation of rubber workers in which individual estimates for a variety of solvents were made on the basis of company records. Bernard and colleagues (1984) found a positive association between lymphatic leukemia and occupational solvents, excluding benzene (OR = 1.56, 95% CI = 0.47–5.17). Among rubber workers, relative risks increased with increasing estimated levels of exposure to mixed solvents (McMichael et al., 1975; Wolf et al., 1981). A cohort study of lymphatic leukemia in nuclear-plant workers found increased risk associated with jobs entailing exposure to unspecified mixtures of organic solvents (RR = 1.99, 95% CI = 0.46–8.67) (Stern et al., 1986).

No conclusions were drawn on an association between exposure to benzene, other specific organic solvents, or unspecified mixtures of solvents and lymphatic leukemia. Table 6.43 identifies the key studies on lymphatic leukemia reviewed by the committee. Unless indicated in the table, the study populations include both men and women.

TABLE 6.43 Selected Epidemiologic Studies—Lymphatic Leukemia and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Studies—Mortality			
Wilcosky et al., 1984	White, male US rubber workers, exposed >1 year	4	2.5
Arp et al., 1983	US rubber workers		
	Primary exposure to benzene	3	4.50
	Secondary exposure to benzene	2	1.50
Case–Control Study			
Bernard et al., 1984	Male residents of Yorkshire, England, ever exposed	NA	3.06 (0.98–11.97)
Other Specific Solvents			
Cohort Study—Mortality			
Wilcosky et al., 1984	White, male US rubber workers, exposed >1 year		
	Acetone	3	6.8
	Ethanol	4	2.0
	Ethyl acetate	3	5.3
	Isopropanol	6	1.8
	Solvent “A” (mixture of toluene and other solvents)	7	2.8
	Specialty naphthas	8	2.8
	Perchloroethylene (tetrachloroethylene)	1	—
	Phenol	1	—
	Toluene	2	3.0
	Trichloroethylene	2	0.81
	VM and P naphthas	3	2.9
	Xylenes	4	3.3
Unspecified Mixtures of Solvents			
Cohort Studies—Mortality			
Stern et al., 1986	Male Portsmouth Naval Shipyard workers		
	Solvent job	NA	1.99 (0.46–8.67)
Arp et al., 1983	US rubber workers		
	Primary exposure to other solvents	11	4.50
	Secondary exposure to other solvent	8	1.60

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Wolf et al., 1981	US rubber workers		
	Low exposure	11	0.8
	Medium exposure	16	1.2
	High exposure	5	1.6
McMichael et al., 1975	Male US rubber workers		
	All exposure levels	NA	3.25
	Low exposure	NA	2.50
	Medium exposure	NA	2.00
	High exposure	NA	5.50
			p-trend <0.025
Case–Control Study			
Bernard et al., 1984	Male residents of Yorkshire, England		
	Solvents (excluding benzene use)	NA	1.56 (0.47–5.17)

NOTE: NA = not available.

Epidemiologic Studies of Exposure to Organic Solvents and Hairy Cell Leukemia

In a study by Clavel and colleagues (1995, 1996, 1998), no excess risks were observed between exposure to benzene and hairy cell leukemia. In another case–control study, exposure to benzene was associated with risk of hairy cell leukemia (Staines and Cartwright, 1993), although CIs included unity (OR = 2.00, 95% CI = 0.50–8.00).

Nordström and colleagues (1998) found an association between hairy cell leukemia and self-reported exposures to white spirit (or naphtha) (OR = 2.0, 95% CI = 1.2–3.4), acetone (OR = 1.2, 95% CI = 0.3–4.3), and trichloroethylene (OR = 1.5, 95% CI = 0.7–3.3).

Clavel and colleagues (1995, 1998) inquired about exposure to organic solvents and found little evidence of an association between hairy cell leukemia and exposure to solvent mixtures or occupations involving exposure to organic solvents, such as painting, spray painting, printing, and laundry and dry cleaning. Staines and Cartwright (1993) also did not find strong evidence of an association with organic solvents (OR = 1.45, 95% CI = 0.58–3.66), while Nordström and colleagues (1998) found positive associations between hairy cell leukemia and exposure to all solvents (OR = 1.5, 95% CI = 0.99–2.3) and working with paints (OR = 4.3, 95% CI = 1.8–10.3).

No conclusions were drawn on an association between exposure to specific solvents or unspecified mixtures of organic solvents and hairy cell leukemia. Table 6.44 identifies the studies related to hairy cell leukemia and solvent exposure. Unless indicated in the table, the study populations include both men and women.

TABLE 6.44 Selected Epidemiologic Studies—Hairy Cell Leukemia and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Case–Control Studies			
Clavel et al., 1996	Male residents of France		
	All exposures to benzene	34	0.8 (0.5–1.2)[a]
	Pure exposure to benzene	2	0.7 (0.1–4.1)[a]
	Painters (exposed to benzene)	4	0.8 (0.2–3.3)[a]
Staines and Cartwright, 1993	Residents of Yorkshire and Trent, UK		
	Benzene, any exposure for any duration	4	2.00 (0.50–8.00)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Other Organic Solvents			
Case–Control Study			
Nordström et al., 1998	Men in the Swedish Cancer Registry, ever exposed		
	White spirit	33	2.0 (1.2–3.4)
	Acetone	3	1.2 (0.3–4.3)
	Trichloroethylene	9	1.5 (0.7–3.3)
Unspecified Mixtures of Organic Solvents			
Case–Control Studies			
Clavel et al., 1998	Male residents of France		
	Any exposure	75	0.9 (0.6–1.3)
	Low intensity	6	1.3 (0.4–4.1)
	Medium intensity	28	0.9 (0.5–1.5)
	High intensity	27	1.0 (0.6–1.8)
	Ever employed as		
	Painters	6	1.0 (0.3–3.0)
	Spray painters	5	2.0 (0.5–8.0)
	Printers	3	1.4 (0.2–8.5)
	Launderers and dry cleaners	1	3.0 (0.2–49.2)
Nordström et al., 1998	Men in the Swedish Cancer Registry, ever exposed		
	All solvents	51	1.5 (0.99–2.3)
	Other solvents	5	2.4 (0.8–7.4)
	Paints	11	4.3 (1.8–10.3)
Clavel et al., 1995	Residents of France, ever exposed		
	Men	107	1.2 (0.8–1.7)
	Women	11	1.1 (0.5–2.4)
Staines and Cartwright, 1993	Residents of Yorkshire and Trent, UK		
	Solvents (any exposure for any duration)	13	1.45 (0.58–3.66)
	Organic chemicals (past exposure to organic solvents, petroleum products, or benzene)	25	1.30 (0.58–2.93)

[a]OR is adjusted for smoking and farming.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) are a group of conditions characterized by abnormalities of the bone marrow cells. Because most of the blood cells produced by these abnormal marrow cells are defective, they are usually destroyed before leaving the bone marrow or shortly after entering the bloodstream, and this results in low blood-cell counts. In about 30% of cases, the bone marrow cells develop further abnormalities and eventually develop into acute leukemia. Therefore, the term *preleukemia*, used in the past to refer to MDS, is not accurate, in that not all patients with MDS develop leukemia.

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Description of Case–Control Studies

All case–control studies of MDS reviewed included interviews with study subjects concerning occupational history, some of which yielded information on specific chemical exposures (Table 6.45). Some studies relied on expert review of questionnaire responses (Ciccone et al., 1993; Nisse et al., 2001; West et al., 1995, 2000) to determine exposures; assessments of exposure in other studies were based on self-reports (Goldberg et al., 1990; Ido et al., 1996; Mele et al., 1994; Nagata et al., 1999; Rigolin et al., 1998). Case–control studies of MDS and exposure to organic solvents that had reasonably good assessments of exposure and enough exposed cases include those by Nisse and colleagues (2001) and West and co-workers (1995).

Epidemiologic Studies of Exposure to Organic Solvents

Although several epidemiologic studies were used to examine the association between mixtures of organic solvents and MDS, in only one cohort study of Chinese workers occupationally exposed to benzene (Hayes et al., 1997), was MDS evaluated; however, cases of MDS were combined with cases of ANLL. An RR of 4.1 (95% CI = 1.4–11.6) was observed, and the relative risk increased as average exposure to benzene increased (RR = 3.2 for constant low-level exposure at under 10 ppm, 7.1 for constant high-level exposure at 25 ppm or higher). This was the first epidemiologic study to demonstrate an association between exposure to benzene and MDS and ANLL.

Earlier case series of benzene-exposed workers noted abnormalities in bone marrow and peripheral blood consistent with MDS specifically (Aksoy and Erdem, 1978; Goguel et al., 1967; Van den Berghe et al., 1979), but the recognition of this disease is relatively recent and has not always been considered in evaluating risks related to exposure to benzene.

Several studies examined the association between exposure to organic solvent mixtures and the risk of MDS. On the basis of qualitative and quantitative assessments of exposure by occupational experts, a study of 204 newly diagnosed cases of MDS and 204 sex- and age-matched controls (Nisse et al., 2001) assessed the association between exposure to solvents and the risk of MDS. Based on 43 exposed cases, the study observed a statistically precise OR of 2.6 (95% CI = 1.6–5.4). That increased risk was supported by the other studies reviewed, including a study of 29 cases exposed to organic solvents (Rigolin et al., 1998) that found an OR of 7.11 (95% CI = 2.42–20.88). Although those exposed to solvents had an increased risk (OR = 7.11. 95% CI = 2.42–20.88), those identified as painters, printers, shoemakers, and chemical-industry workers combined did not (OR = 0.81, 95% CI = 0.33–2.00). The study by Mele and colleagues (1994) found high odds ratios for shoemakers and painters individually (OR = 4.3, 95% CI = 0.9–21.1 and OR = 5.4, 95% CI = 0.5–61.0, respectively). The numbers of exposed cases were extremely small, as evidenced by the wide CIs, and the case definition of MDS included those with refractory anemia who had an excess of blasts; this made the health-outcome assessment less precise.

Studies by West and colleagues (2000) and Nagata and colleagues (1999) found increased risks of MDS among residents of the UK (OR = 1.8, 95% CI = 0.6–6.0) and Japan (OR = 1.99, 95% CI = 0.97–4.10), respectively. An earlier study in Japan (Ido et al., 1996) also showed increased risks of MDS in men and women exposed to organic solvents occupationally (OR = 1.50, 95% CI = 0.85–2.64).

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TABLE 6.45 Description of Case–Control Studies of Myelodysplastic Syndromes and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Goldberg et al., 1990	Cases, age 28–88 years, referred to the hematology–oncology division of the Medical College of Pennsylvania in 1976–1989 with hematologic confirmation; controls selected from the primary-care and cardiology clinics of the same hospital, matched for age, sex, and socioeconomic group	52	52	Solvents	Questionnaire developed by the American Lung Association to assess occupational history and lifetime exposure to solvents (self-reports)	Fisher exact test	None
Ciccone et al., 1993	Cases, age 15–74 years, treated in the Main Hospital of Torino, Italy, newly diagnosed in 1989–1990; hospital controls selected in the same interval, matched for sex, age, and area of residence; population controls randomly selected from residents of Torino, matched on above Response rates: 91% of cases; 99% of hospital controls; 82% of population controls	19	246	Benzene Solvents	Interview with standardized questionnaire to assess lifetime occupational history with exposure to solvents determined by industrial hygienist	Logistic regression	Age, area of residence and of birth, smoking
Mele et al., 1994	Cases, age 15 years or over, identified by hematology departments in three Italian cities in 1986–1990; outpatients without hematological disorders selected as controls	111 (refractory anemia with excess of blasts)	1161	Painting work Shoemakers	In-hospital interview to assess lifetime behavioral and occupational exposure histories (self-reports)	Logistic regression	Age, sex, education, residence outside study town, other occupations
West et al., 1995	Cases, age 15 years or more, from areas of the UK; controls selected from outpatient clinics and inpatient wards, matched for age, sex, area of residence and hospital, and year of diagnosis (see also West et al., 2000)	400	400	Solvents	In-person interview with questionnaire to assess lifetime occupational and exposure history, duration and intensity of exposure (self-reports)	Matched pairs analysis	Matching variables

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Ido et al., 1996	Cases, age 20–74 years, selected from 32 hospitals in Japan in 1992–1993 with hematologic confirmation; controls selected from outpatient departments of each hospital, matched for age, sex, and hospital	116	116	Organic solvents	Self-administered questionnaire to assess lifetime employment in specific occupations; exposure to solvents was determined from a list of occupations with probable or possible exposure	Conditional logistic regression	Matching variables
Rigolin et al., 1998	Consecutive cases referred to the Institute of Haematology of Ferrara, Italy, in 1990–1996 with hematologic confirmation; controls randomly selected from institute outpatients, matched for sex, date of birth, and geographic area	178	178	Solvents Occupational exposure: painters, printers, shoemakers, chemical industry	In-person or telephone interview with questionnaire to assess types and duration of exposure (self-reports)	Unadjusted OR	None
Nagata et al., 1999	Cases, age 20–74 years, selected from 28 institutes in Japan in 1995–1996 with hematologic confirmation; controls selected through use of telephone directories, matched for sex and prefecture	111	830	Organic solvents	Self-administered questionnaire to assess occupational exposure to solvents (self-reports)	Conditional logistic regression	Matching variables, age
West et al., 2000	Cases, age 15 years or over, from three specialist regional centers in the UK; controls selected from outpatients, matched for age, sex, and area of residence (see also West et al., 1995)	400	400	Organic chemicals	In-person interview with questionnaire to assess lifetime occupational and exposure history, duration and intensity of exposure	Matched pairs analysis	Matching variables
Nisse et al., 2001	Cases diagnosed in the hematology department of the University Hospital of Lille, France, in 1991–1996 with hematologic confirmation; controls randomly selected from electoral registers, matched for sex and age	204	204	Solvents	In-person interview with questionnaire to assess lifetime occupational history; exposure to solvents was determined by a team of experts	Mantel-Haenszel	Matching variables

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Summary and Conclusion

All but one (Goldberg et al., 1990) of the studies reviewed by the committee and identified below in Table 6.46 found consistently positive odds ratios for the association between MDS and exposure to unspecified mixtures of organic solvents. Given that all the studies reviewed are case–control studies, almost all relied exclusively on self-reported exposures, which may be subject to recall bias. The difficulty in classifying MDS accurately and consistently is another limitation that the committee considered in evaluating the literature.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and myelodysplastic syndromes.

For exposure to specific solvents, such as benzene, the rarity of the disease and the difficulty in classifying MDS as a separate entity have limited the evaluation of associations in most studies. Additional studies are needed to elucidate and support the association between exposure to benzene and MDS. They should also attempt to separate MDS from other cancers, such as ANLL, so that the relationship between exposure to benzene and MDS can be further understood. Table 6.46 identifies the studies related to MDS and solvent exposure. Unless indicated in the table, the study populations include both men and women.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to benzene and myelodysplastic syndromes.

TABLE 6.46 Selected Epidemiologic Studies—Myelodysplastic Syndromes and Exposure to Organic Solvents

Reference	Study description	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Study—Incidence			
Hayes et al., 1997	Chinese factory workers		
	ANLL or MDS		
	All unexposed	4	1.0
	All exposed	28	4.1 (1.4–11.6)
	Rubber workers	2	6.1
	Chemical workers	4	4.5
	Constant exposure, ANLL or MDS		
	<10 ppm	10	3.2 (1.0–10.3)
	10–24 ppm	4	5.1 (1.3–20.6)
	≥25 ppm	8	7.1 (2.1–23.7)
			p-trend = 0.0003
Unspecified Mixtures of Organic Solvents			
Case–Control Studies			
Nisse et al., 2001	Residents of northern France		
	Solvents, ever exposed	43	2.6 (1.6–5.4)
	Glue adhesives, ever exposed	11	2.8 (0.8–11.8)
West et al., 2000	Residents of the UK		
	Organic chemicals, >50 hours of exposure at moderate intensity	75	1.8 (0.6–6.0)

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Reference	Study description	Exposed Cases	Estimated Relative Risk (95% CI)
Nagata et al., 1999	Residents of Japan		
	Organic solvents, occupational exposure		
	Males and females	12	1.99 (0.97–4.10)
	Males	9	1.66 (0.74–3.73)
Rigolin et al., 1998	Residents in Ferrara, Italy		
	Solvent, ever exposed	25	7.11 (2.42–20.88)
	Occupational exposure (painters, printers, shoemakers, chemical industry)	9	0.81 (0.33–2.00)
Ido et al., 1996	Residents of Japan		
	Organic solvents, occupational exposure		
	Males and females	42	1.50 (0.85–2.64)
	M ales	34	1.28 (0.69–2.36)
	Females	8	3.50 (0.73–16.8)
West et al., 1995	Residents of the UK		
	Solvents, low threshold	38	1.03
	Solvents, medium threshold	17	0.89
	Solvents, high threshold	11	1.22
Mele et al., 1994	Residents of Italy		
	Shoemakers	3	4.3 (0.9–21.1)[a]
	Painters	2	5.4 (0.5–61.0)[a]
Goldberg et al., 1990	Residents of Pennsylvania		
	Solvents, ever exposed	5	0.35 (0.08–1.54)[b]

[a]Includes refractory anemia with excess of blasts. [b]Risk estimate and 95% CI calculated by the committee using standard methods from the observed and expected numbers presented in the original study.

CHILDHOOD CANCER

Early studies of parental occupation and childhood cancers followed from work by Fabia and Thuy (1974), who found an association between paternal hydrocarbon-related occupations and childhood cancer. A number of studies have since examined potential exposures to hydrocarbons (e.g., DeRoos et al., 2001; Johnson et al., 1987; Van Steensel-Moll, 1985; Zack et al., 1980), and others have focused on parental exposure to solvent mixtures (e.g., Cordier et al., 1997; Smulevich et al., 1999; Shu et al., 1999) as a potential risk factor. Given that the committee was charged with evaluating exposures that occurred during the Gulf War and that soldiers, if they were determined to be pregnant, were removed from the area immediately, the committee did not review studies that considered exposure during pregnancy or after the birth of a child; those studies were not considered directly relevant to the exposure period of interest for this review. Instead, the committee focused its evaluation and conclusions on studies that analyzed preconception exposures. Discussion of the rationale for that exclusion criterion is in Chapter 5 in the childhood cancer section.

Description of Case–Control Studies

Studies of parental occupational exposure and childhood cancer have relied on four approaches to determine exposure: use of occupation or industry as surrogates of exposure, self-reporting of specific exposure, the use of a job–exposure matrix, and review of occupational-

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history information by an industrial hygienist. Most case–control studies relied on the use of occupational or industrial titles as indexes of exposure. The childhood cancers that were examined include brain tumors (Cordier et al., 1997), leukemia (Lowengart et al., 1987), neuroblastoma (Olshan et al., 1999), and multiple cancers simultaneously (Smulevich et al., 1999). Other case–control studies of childhood cancer used self-reported exposure, including studies of leukemia (Lowengart et al., 1987) or specific subtypes of leukemia—ANLL (Buckley et al., 1989) and ALL (Shu et al., 1999)—and of neuroblastoma (De Roos et al., 2001). A smaller number of studies either used a job–exposure matrix (Cordier et al., 1997; Feingold et al., 1992; Smulevich et al., 1999) or relied on expert review by industrial hygienists (De Roos et al., 2001; Olshan et al., 1999). Table 6.47 describes the study design characteristics of each of the case–control studies reviewed by the committee.

Epidemiologic Studies of Exposure to Organic Solvents and Childhood Leukemia

The literature consisted of studies that analyzed all types of childhood leukemia together and studies that focused on specific leukemia cell types. The committee reported the findings as presented in the literature.

In one cohort study, paternal exposure (Feychting et al., 2001) to solvents and benzene was determined by linking the fathers' occupational information with a job–exposure matrix; increased RRs of 1.25 for exposure to solvents (95% CI = 0.80–1.95) and 1.23 for exposure to benzene (95% CI = 0.39–3.85) were found. The exposure period was defined as the period 2–26 months before the child's birth, which includes both preconception and pregnancy-related exposure. As a result, the study is not completely relevant to this review, given the committee's focus on preconception exposures.

Two case–control studies examined both maternal and paternal exposures (Lowengart et al., 1987; Smulevich et al., 1999). In a Russian case–control study (Smulevich et al., 1999), maternal occupational exposure to solvents was found to have an OR of 3.1 (95% CI = 1.5–6.3). An increased risk of childhood leukemia was also found to be associated with paternal occupational exposure to solvents prior to conception (OR = 1.4, 95% CI = 0.95–2.1). In a case–control study in Los Angeles County, Lowengart and colleagues (1987) found associations with preconception paternal exposure to chlorinated solvents (OR = 2.2, $p = 0.09$), trichloroethylene (OR = 2.0, $p = 0.16$), and methyl ethyl ketone (OR = 1.7, $p = 0.24$). Mothers of too few cases were occupationally exposed for analysis in this study.

Shu and colleagues (1999) conducted an extensive study of children with ALL and found an association with mothers' self-reports of exposure to any solvents (OR = 1.8, 95% CI = 1.3–2.5), to chlorinated solvents (OR =1.8, 95% CI = 0.2–20.8), to nonchlorinated organic solvents (OR = 2.0, 95% CI = 1.0–4.2), to trichloroethylene (OR = 1.8, 95% CI = 0.6–5.2), to tetrachloroethylene (OR = 1.4, 95% CI = 0.2–8.6), to toluene (OR = 1.5, 95% CI = 0.6–3.8), and to paint remover (OR = 2.5, 95% CI = 1.0–5.9), but not with exposure to benzene (OR = 0.7, 95% CI = 0.3–1.8) or to methyl ethyl ketone (OR = 0.8, 95% CI = 0.3–1.9). For preconception paternal exposure, associations were found with exposure to nonchlorinated, organic solvents (OR = 1.3, 95% CI = 0.8–1.9) and to benzene (OR = 1.2, 95% CI = 0.8–1.2), but no associations were found with other exposures. Feingold and colleagues (1992) found increased risks of ALL associated with paternal exposure to solvents (OR = 1.7, 95% CI = 0.4–8.2), to benzene (OR = 1.6, 95% CI = 0.5–5.8), and to diethylene glycol (OR = 1.4, 95% CI = 0.4–4.5) in the year before birth.

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TABLE 6.47 Description of Case–Control Studies of Childhood Cancer and Exposure to Organic Solvents

Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Lowengart et al., 1987	Cases, age 10 years and under, identified from the Los Angeles County Cancer Surveillance Program in 1980–1984; controls selected from friends of case children or through RDD, matched on age, sex, and race (including native Spanish-speaking Caucasians) Participation rate: 79% of cases	123 leukemia	123	Trichloroethylene MEK Chlorinated solvents	Telephone interview with questionnaire to assess parental occupational and exposure history (self-reports)	Matched pairs	Matching variables
Buckley et al., 1989	Cases, age under 18 years, selected from the Childrens Cancer Study Group with diagnosis in 1980–1984; controls selected through RDD, matched for date of birth and race	204 ANLL	204	Solvents	Telephone interviews used to assess lifetime occupational history (job titles) and exposure contacts of parents	Conditional logistic regression	Matching variables
Feingold et al., 1992	Cases, age 14 years or under, identified through the Colorado Central Cancer Registry of Denver residents diagnosed in 1976–1983 with almost complete histologic confirmation; controls selected through RDD, matched for age, sex, and telephone exchange area Participation rates: 70.8% of cases, 79.9% of controls	59 ALL 48 brain	222	Benzene Diethylene glycol Solvents	In-person or telephone interview with questionnaire to assess parental occupational history (job–industry titles); job–exposure matrix used to assess exposures	Mantel-Haenszel	Father's education
Cordier et al., 1997	Cases, age 15 years or under, identified in centers in Paris, Milan, and Valencia with partial histologic verification (72–87% complete); population controls selected from census information or local health-service records, depending on location, selectively matched for year of birth, sex, and area of residence	251 brain	601	Solvents	In-person interviews to assess parental occupations (job titles) held from 5 years before the child's birth; job–exposure matrix used to assess exposures	Unconditional logistic regression	Child's age, sex, exposure to tobacco and ionizing radiation, mother's age, years of schooling
Olshan et al., 1999	Cases, age under 19 years, selected from the Childrens Cancer Group and Pediatric Oncology Group with diagnosis in 1992–1996; controls selected through RDD, matched for date of birth Participation rates: 73% of cases, 74% of controls	504 neuro-blastoma	504	Painter (paternal occupation)	Telephone interview to assess parental occupational and exposure history (job–industry titles)	Conditional logistic regression	Maternal race, maternal age, maternal education, household income

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Reference	Description of Study Population	Number of Cases	Number of Controls	Relevant Exposure(s)	Determination of Exposure	Analysis	Adjustment for Confounding
Shu et al., 1999	Cases, age under 15 years, diagnosed by a Children's Cancer Group member or affiliated institution in 1989–1993; controls selected through RDD, matched for age, race, and telephone area code and exchange Participation rates: 92% of cases, 76.5% of controls	1842 ALL	1986	Benzene Paint remover Chlorinated solvents Nonchlorinated solvents Any solvents	Telephone interview to assess parental occupations (job–industry titles) and exposure history (self-reports)	Conditional and unconditional logistic regression	Matching variables, maternal and paternal education, sex, family income
Smulevich et al., 1999	Cases, age 14 years and under, identified from the Moscow Central Cancer Dispensary in 1986–1988; controls randomly selected from records of local pediatric polyclinics in Moscow, matched for age, sex, and residence	593 cancers (number of leukemia cases not specified)	1181 healthy controls	Solvents	In-person interview with questionnaire to assess parental lifetime occupational histories (job titles); exposure to solvents derived from job–exposure matrixes	Conditional logistic regression	Parental alcohol consumption
De Roos et al., 2001	Cases, age under 19 years, selected from the Childrens Cancer Group and Pediatric Oncology Group with diagnosis in 1992–1994; controls selected through RDD, matched for date of birth (see also Olshan et al., 1999) Participation rates: 73% of cases, 74% of controls (Followup of Olshan et al., 1999)	504 neuro-blastoma	504	Trichloroethylene Benzene Xylene Acetone MEK Alcohols Halogenated hydrocarbons Volatile hydrocarbons	Telephone interview to assess parental occupational and exposure history (self-reports) with coded exposure based on industrial hygienist review	Unconditional logistic regression	Child's age, maternal race, maternal age, maternal education

NOTE: ALL = acute lymphocytic leukemia; ANLL = acute nonlymphoblastic leukemia; MEK = methyl ethyl ketone; RDD = random-digit dialing

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Only one study investigated ANLL in conjunction with preconception solvent exposure (Buckley et al., 1989). On the basis of self-reported exposure, a positive association between ANLL and paternal solvent exposure before pregnancy (OR = 2.2, $p < 0.05$) was found. No estimates of relative risk for maternal exposure to solvents were presented.

Summary and Conclusion

The studies on childhood leukemia and exposure to organic solvents generally followed similar procedures for ascertaining cases, matching controls, and interviewing parents to obtain relevant information. Studies generally controlled for known confounders, but in most cases risk factors are not well understood. Studies that examined parental occupational exposure often did not differentiate whether the exposure occurred before, during, or after pregnancy. Little information was available on preconception exposure for each cancer type. Exposure measures were based largely on interviews and, thus, were subject to recall bias or random misclassification of exposures; the former tends to artificially increase the odds ratio, and the latter attenuates toward the null value. Many of the studies presented the additional concern that mothers who reported on their husbands' work exposure further increased the likelihood of misclassification of the fathers' exposure.

For childhood leukemias combined, several studies showed positive associations with exposure to solvents. Several studies were limited by misclassification bias related to self-reporting of exposure and by the fact that some looked at all childhood leukemias and others focused on specific cell types, such as ALL and ANLL. Given the combination of the limitations of this body of evidence and the consistently positive findings, the committee was unable to reach a consensus conclusion. Some committee members believed that the evidence fulfilled the category of inadequate/insufficient, while others believed it was limited/suggestive of an association. Future studies that address some of the limitations identified above are needed to understand the association between childhood leukemia and exposure to solvents. Table 6.48 identifies all the studies evaluated by the committee.

TABLE 6.48 Selected Epidemiologic Studies—Childhood Leukemia and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Leukemia (all types)			
Cohort Study—Incidence			
Feychting et al., 2001	Children in Sweden		
	Paternal preconception exposure		
	Solvents	23	1.25 (0.80–1.95)
	Benzene	3	1.23 (0.39–3.85)
Case–Control Studies			
Smulevich et al., 1999	Children in Moscow		
	Occupational exposure before conception		
	Maternal exposure to solvents	20	3.1 (1.5–6.3)
	Paternal exposure to solvents	70	1.4 (0.95–2.1)
Lowengart et al., 1987	Children in Los Angeles County		
	Paternal preconception exposure		
	Chlorinated solvents	9	2.2 ($p = 0.09$)
	Trichloroethylene	6	2.0 ($p = 0.16$)
	Methyl ethyl ketone	5	1.7 ($p = 0.24$)

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Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Acute Lymphocytic Leukemia			
Case–Control Studies			
Shu et al., 1999	Children diagnosed through the Children's Cancer Group		
	Maternal preconception exposure, any solvents	93	1.8 (1.3–2.5)
	Chlorinated solvents	2	1.8 (0.2–20.8)
	Nonchlorinated organic solvents	22	2.0 (1.0–4.2)
	Benzene	7	0.7 (0.3–1.8)
	Trichloroethylene	9	1.8 (0.6–5.2)
	Tetrachloroethylene	3	1.4 (0.2–8.6)
	Methyl ethyl ketone	9	0.8 (0.3–1.9)
	Toluene	5	1.5 (0.6–3.8)
	Naphtha	2	0.5 (0.1–3.0)
	Paint remover	16	2.5 (1.0–5.9)
	Paternal preconception exposure, any solvents	490	1.1 (0.9–1.3)
	Chlorinated solvents	9	1.0 (0.4–2.5)
	Nonchlorinated organic solvents	61	1.3 (0.8–1.9)
	Benzene	74	1.2 (0.8–1.2)
	Trichloroethylene	100	1.1 (0.8–1.5)
	Tetrachloroethylene	21	0.8 (0.5–1.5)
	Methyl Ethyl Ketone	107	1.1 (0.8–1.5)
	Toluene	82	1.1 (0.8–1.5)
	Xylene	67	1.2 (0.8–1.8)
	Naphtha	62	1.2 (0.8–1.7)
	Paint remover	120	1.0 (0.7–1.3)
Feingold et al., 1992	Children in the Denver, CO, area		
	Paternal occupational exposure year before birth		
	Solvents	3	1.7 (0.4–8.2)
	Benzene	9	1.6 (0.5–5.8)
	Diethylene glycol	7	1.4 (0.4–4.5)
Acute Nonlymphocytic Leukemia			
Case–Control Study			
Buckley et al., 1989	Children diagnosed through the Children's Cancer Group		
	Paternal preconception exposure, solvents	NA	2.2 (p <0.05)

NOTE: NA = not applicable.

Epidemiologic Studies of Exposure to Organic Solvents and Neuroblastoma

Olshan and colleagues (1999) reported an increased risk of neuroblastoma in children whose fathers were painters (OR = 2.1, 95% CI = 0.9–4.8); this was the most relevant of the 73 paternal occupations listed for solvent exposure. In a followup study, the investigators used a job–exposure matrix to evaluate maternal and paternal occupational exposure to 65 chemical compounds or broad categories of substances (De Roos et al., 2001). As reviewed by an industrial hygienist, neuroblastoma risk was not markedly increased based on maternal exposures to halogenated hydrocarbons (OR = 0.7, 95% CI = 0.2–2.1), to volatile hydrocarbons (OR = 1.2, 95% CI = 0.7–2.1), to acetone (OR = 1.1, 95% CI = 0.4–2.8), or to alcohols (OR = 1.0, 95% CI = 0.5–2.1). However, for paternal exposures, risk estimates were higher: volatile hydrocarbons (OR = 1.5, 95% CI = 1.0–2.1), alcohols (OR = 1.8, 95% CI = 0.9–3.3), benzene (OR = 2.0, 95% CI = 0.4–10.3), methyl ethyl ketone (OR = 1.4, 95% CI = 0.5–3.8), naphtha (OR = 1.4, 95% CI = 0.4–5.9), and xylene (OR = 1.4, 95% CI = 0.5–4.3). Paternal exposure to acetone,

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trichloroethylene, tetrachloroethylene, methylene chloride, and chloroform did not show increased risks.

Summary and Conclusion

The two studies identified were well-conducted. They evaluated a large number of neuroblastoma cases and possible exposures, while considering the possibility of recall bias. However, other corroborating studies are needed to clarify whether an association exists. Table 6.49 identifies the study reviewed by the committee for neuroblastoma.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between either maternal or paternal preconception exposure to solvents under review and neuroblastoma.

TABLE 6.49 Selected Epidemiologic Studies—Childhood Neuroblastoma and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Neuroblastoma			
Case–Control Studies			
De Roos et al., 2001	Children registered at Children's Cancer Group or Pediatric Oncology Group hospitals		
	Occupational exposure in the 2 years before child's birth[a]		
	Maternal exposure		
	Halogenated hydrocarbons	6	0.7 (0.2–2.1)
	Volatile hydrocarbons	27	1.2 (0.7–2.1)
	Acetone	9	1.1 (0.4–2.8)
	Alcohols	14	1.0 (0.5–2.1)
	Paternal exposure		
	Halogenated hydrocarbons	34	0.9 (0.5–1.5)
	Trichloroethylene	9	0.9 (0.3–2.5)
	Volatile hydrocarbons	122	1.5 (1.0–2.1)
	Acetone	23	0.9 (0.5–1.7)
	Benzene	5	2.0 (0.4–10.3)
	Methyl ethyl ketone	12	1.4 (0.5–3.8)
	Xylene	10	1.4 (0.5–4.3)
	Tetrachloroethylene	4	0.5 (0.1–1.7)
	Methylene chloride	4	0.7 (0.2–2.8)
	Chloroform	3	1.2 (0.2–7.5)
	Alcohols	49	1.8 (0.9–3.3)
	Naphtha	11	1.4 (0.4–5.9)
Olshan et al., 1999	Children registered at Children's Cancer Group or Pediatric Oncology Group hospitals		
	Paternal occupation—painter	18	2.1 (0.9–4.8)

[a]Industrial hygienist-reviewed exposure information.

Epidemiologic Studies of Exposure to Organic Solvents and Brain Cancer

A European case–control study of brain cancer and parental occupation found that "high" maternal occupational exposure to solvents was strongly associated with an increased risk of brain cancer (OR = 2.4, 95% CI = 1.2–4.9) and primitive neuroectodermal tumor (PNET) (OR =

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3.2, 95% CI = 1.0–10.3); estimates of risk of astroglial tumors were also increased for "high" levels of exposure to solvents (OR = 2.3, 95% CI = 0.9–5.8) and other glial tumors were not (OR = 0.8, 95% CI = 0.1–6.6) (Cordier et al., 1997). Like maternal exposure, high paternal exposure to solvents was associated with increased risk of brain cancer (OR = 1.2, 95% CI = 0.7–1.9) and astroglial tumors (OR = 1.3, 95% CI = 0.7–2.3), but not other glial tumors (OR = 0.4, 95% CI 0.1–1.4). A second case–control study of childhood brain cancer and paternal occupational exposure showed no association with exposure to benzene (OR = 0.7, 95% CI = 0.1–3.1) (Feingold et al., 1992). However, an association was found with exposure to solvents (OR = 1.2, 95% CI = 0.2–8.5) and diethylene glycol (OR = 1.3, 95% CI = 0.3–5.2).

Summary and Conclusion

On the basis of those two case–control studies, the committee decided that the body of evidence was too small and inconsistent in outcome (brain cancer broadly vs PNET vs astroglial tumors). Table 6.50 identifies the studies reviewed by the committee in drawing its conclusion.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between either maternal or paternal preconception exposure to solvents under review and childhood brain cancers.

TABLE 6.50 Selected Epidemiologic Studies—Childhood Brain Cancers and Exposure to Organic Solvents

Reference	Study Population	Exposed Cases	Estimated Relative Risk (95% CI)
Brain Cancer			
Case–Control Studies			
Cordier et al., 1997	Children in Milan, Paris, and Valencia		
	Occupational exposure in the 5 years before birth		
	Maternal exposure to solvents		
	Medium level, brain cancer	30	1.0 (0.6–1.7)
	High level, brain cancer	19	2.4 (1.2–4.9)
	Medium level, PNET	7	1.3 (0.5–3.3)
	High level, PNET	5	3.2 (1.0–10.3)
	Medium level, astroglial tumors	15	1.1 (0.6–2.1)
	High level, astroglial tumors	9	2.3 (0.9–5.8)
	Medium level, other glial tumors	6	0.9 (0.3–2.6)
	High level, other glial tumors	1	0.8 (0.1–6.6)
	Paternal exposure to solvents		
	Medium level, brain cancer	40	0.9 (0.6–1.5)
	High level, brain cancer	37	1.2 (0.7–1.9)
	Medium level, PNET	16	2.3 (1.1–4.9)
	High level, PNET	9	1.7 (0.7–4.1)
	Medium level, astroglial tumors	23	1.1 (0.6–2.0)
	High level, astroglial tumors	24	1.3 (0.7–2.3)
	Medium level, other glial tumors	10	1.3 (0.6–3.0)
	High level, other glial tumors	3	0.4 (0.1–1.4)
Feingold et al., 1992	Children in the Denver, CO, area		
	Paternal occupational exposure year before birth		
	Benzene	4	0.7 (0.1–3.1)
	Solvents	2	1.2 (0.2–8.5)
	Diethylene glycol	7	1.3 (0.3–5.2)

NOTE: PNET = primitive neuroectodermal tumors

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7

NEUROLOGIC EFFECTS

Neurologic effects are difficult to diagnose because of variability in signs and symptoms, difficulty in interpreting neurologic test results, and lack of biologic markers of many symptoms related to the nervous system. The nonspecificity of symptoms often makes it difficult to draw etiologic conclusions on the basis of a single test or measure of nervous system function. That is true especially of chronic environmental exposures (Grandjean et al., 1991), and it presents challenges for the clinician in making neurologic diagnoses (Juntunen, 1982).

The nervous system is functionally and anatomically divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord. The PNS includes nerve roots, the brachial and lumbar plexuses, and the peripheral nerves that pass to the extremities. The peripheral nerves innervate muscles, convey sensory information to the CNS, and contain autonomic fibers that regulate the activity of the heart, blood vessels, sweat glands, bladder, and intestines. Environmental assaults on the CNS can lead to neurobehavioral abnormalities, such as cognitive and neuropsychiatric disorders, and to disturbances related to attention, memory, perception, anxiety, mood, sensation, weakness, tremors, reaction time, and abnormal movement. Assaults on the PNS can lead to peripheral neuropathy also known as polyneuropathies; however, neuropathies can be a feature of many common medical disorders, such as the neuropathy associated with diabetes.

The senses (such as vision, hearing, balance, taste, and smell) depend on neural pathways that originate in peripheral receptors and terminate in the cerebral cortex, brainstem, or spinal cord. Chemical agents that affect the senses often interfere with peripheral sensory receptors (Spencer et al., 2000). And many diseases of the nervous system might have environmental etiologies, such as Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease. All of the studies evaluated in this chapter examine the relationship between insecticide or solvent exposure and neurologic effects.

Clinicians diagnose neurologic diseases and disorders by administering neurologic tests. Numerous tests of neurologic function are discussed in this chapter. The neurologic examination comprises comprehensive social and medical histories, clinical tests of nervous system function, detailed neurobehavioral test batteries (Appendix F), laboratory examinations, and other ancillary tests. The results need to be integrated and analyzed critically to ensure a valid assessment. Performance on neurologic tests and neurobehavioral test batteries may be influenced by a host of confounding factors, including medications,

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alcohol, age, education, motivation and culture, and the presence of comorbid conditions (such as diabetes, depression, and cardiovascular disease).

The committee reviewed the epidemiologic literature on neurologic effects of insecticide and solvent exposure, focusing on studies that examined long-term effects. Four general types of neurologic effects are examined in this chapter: peripheral neuropathy, neurobehavioral effects (assessed by symptom reporting or performance on validated neurobehavioral tests or batteries), neurologic diseases, and sensory effects. For each, the chapter covers studies of Gulf War veterans, when available, and studies of occupational exposure to insecticides and to solvents.

Almost all the available studies of exposure to insecticides focus on exposures to insecticides as a broad group, to insecticide mixtures, or to organophosphorous (OP) insecticides in particular. Similarly, studies of exposure to solvents often examined solvents as a broad group, solvent mixtures, or workers in occupations that were exposed to the solvents of interest (Chapter 2).

The committee was unable to identify epidemiologic studies of sufficient quality to permit a separate evaluation of the long-term neurologic effects of pyrethrins, carbamates, organochlorines, or the insect repellent *N,N*-diethyl-3-methylbenzamide (DEET). The evidence base for many of those pesticides and neurologic effects generally consisted of case reports and case series—study designs that do not carry the methodologic rigor of cross-sectional, cohort, or case–control studies. Several of the OP-insecticide studies evaluated in this chapter, where noted, did include mixed exposures to OPs and carbamates but not of carbamates alone. The committee was not able to draw conclusions about long-term effects of pesticides other than OP insecticides, because of the lack of methodologically rigorous studies. The effects of pesticides are covered in greater detail in Chapter 3.

The committee reviewed hundreds of peer-reviewed and published studies of neurologic effects of insecticides and solvents, and it selected for detailed evaluation only the studies that met its inclusion criteria, which are listed below.[1]

- The study had to be a published in a peer-reviewed journal and had to have methodologic rigor, including a control or reference group, and reasonable control for confounders. Case studies and case series were generally excluded from the committee's consideration.
- The study had to identify insecticides and solvents relevant to the committee's charge (Chapters 1 and 2). If solvents were not identified, for example, the study may have been included if it examined occupations with presumed exposure to many of the solvents sent to the Gulf War. For example, studies of painters, workers in paint manufacturing, printers, dry cleaners, or workers in boot or shoe manufacturing and repair were included in the committee's assessment.
- For some neurologic effects, the committee only considered studies that examined long-term rather than short-term effects. That was accomplished typically by examining studies that analyzed only past exposure—by requiring an exposure-free interval of

[1]Additional criteria, specific for particular neurologic effects, are listed in the appropriate sections of the chapter.

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weeks to months before testing of study subjects. (The next section describes the rationale for this criterion.)

As the committee reviewed the body of evidence, it was apparent that some studies of multiple outcomes could provide strong evidence for one of the outcomes and only weak evidence for another. For example, a study that was well-designed for assessing a neurobehavioral effect might not have been as well-designed for assessing peripheral neuropathy.

Short-Term vs Long-Term Effects

The committee evaluated long-term effects because they are most relevant to veterans whose exposures occurred during the Gulf War but whose symptoms persisted for months or years after cessation of exposure (Appendix A). Long-term effects of a given exposure can be distinct from short-term effects. For example, OP-insecticide exposure produces a well-defined short-term effect, the acute cholinergic syndrome (Chapter 3); this life-threatening syndrome is quite different in characteristics and severity from the long-term effects considered in this chapter.

Occupational studies of neurologic effects often do not permit the distinction between long-term effects (months or years) and short-term effects (hours to weeks), because many studies examine workers with both past and current (ongoing) exposure. Consequently, if a study finds a neurologic effect, it is difficult to determine whether the observed effect will persist or disappear on cessation of the exposure unless an exposure-free interval of weeks or months has passed before the effect is measured. Many of the studies reviewed by the committee were not designed to determine whether an effect was a long-term or short-term one.

The challenge of distinguishing long-term and short-term effects is greater for examining neurobehavioral effects than neurologic diseases, for reasons related to onset, reversibility, and availability of objective testing. Neurobehavioral effects (such as symptoms of memory loss and fatigue) can be short-term effects, long-term effects, or both; they can appear within hours of exposure or later; and they can persist or disappear after cessation of exposure. Neurobehavioral effects cannot usually be verified with pathologic or biochemical tests. Conversely, neurologic diseases are generally believed to be irreversible after a confirmed diagnosis and are associated with abnormal results of pathologic or biochemical tests. Thus, in evaluating the body of evidence specifically on long-term neurobehavioral effects, the committee required that an exposure-free interval of weeks to months elapse before testing. The committee also held sensory effects to that standard because sensory effects can also be reversible. For studies of peripheral neuropathy and neurologic diseases, the committee did not require an exposure-free interval, because these neurologic effects are almost always long-term effects (although some degree of recovery or lack of progression is possible).

Short-Term vs Long-Term Effects of Organophosphorous (OP) Compounds

The most immediate short-term effect of high OP exposure is known as the acute cholinergic syndrome. Its signs and symptoms are recognizable within minutes to hours and include pinpoint pupils, salivation, severe nausea, vomiting, and diarrhea. The acute cholinergic syndrome, which is highly dose-dependent, requires emergency care to prevent

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respiratory failure and death (Chapter 3). About 10–20% of people who survive an acute poisoning episode are at risk for the intermediate syndrome, which can appear within 16–20 hours after exposure to the insecticide (Shailesh et al., 1994) or 7–75 hours after the onset of acute poisoning (He et al., 1998). Marked by weakness of neck flexors and proximal limb muscles, the intermediate syndrome is also life-threatening and requires hospitalization (Chapter 3), but it resolves after 30–40 days and so cannot be characterized as a long-term effect (Lotti, 2001).

High OP-insecticide exposure is presumed to have occurred if a person displays the acute cholinergic syndrome. High and low OP-insecticide exposure can be confirmed by assessment of the biomarker acetylcholinesterase (AChE). The degree of AChE inhibition is both an effect of recent OP-pesticide exposure and a measure of the magnitude of the exposure. The degree of AChE inhibition is best interpreted by comparing a person's postexposure and pre-exposure (baseline) red-cell AChE concentrations. A reduction of 20–30% is considered an objective indication of recent OP exposure, and a reduction of 50–70% generally confirms clinical OP poisoning. If a person's baseline value is unavailable, other methods can be used. One is to compare the person's value with a population mean; however, because of population variability, this comparison is less reliable. Another is to compare the increase in AChE several months after recovery from poisoning; this indirect method measures how much a person's AChE was depressed at the time of acute poisoning (Coye et al., 1986). Serum cholinesterase (such as butyrylcholinesterase) values have less utility because their functional significance is unknown, and there is a wider range of normal values.

GULF WAR VETERANS STUDIES

A number of studies have shown that Gulf War veterans have much higher rates of fatigue, headache, pain, and cognitive symptoms than nondeployed military personnel in several countries, including the United States (Iowa Persian Gulf Study Group, 1997; Kang et al., 2000), United Kingdom (Cherry et al., 2001a; Unwin et al., 1999), and Canada (Goss Gilroy Inc., 1998). Veterans' symptoms are discussed in this chapter because they are most closely related to nervous system function, yet they are characterized as "unexplained illnesses" because they do not fit established diagnoses (IOM, 2000).

The committee reviewed epidemiologic studies of Gulf War veterans (Appendix A). For the purposes of this chapter, the committee sought to answer these questions: What are the nature and quality of the evidence that specifically links solvent or insecticide exposures during the Gulf War to long-term neurologic effects?[2] Is the evidence strong enough to justify particular conclusions regarding Gulf War veterans, or can it be marshaled to support the committee's conclusions drawn from other populations, mostly workers with occupational exposure to relevant pesticides or solvents? To answer those questions, the committee focused its evaluation on the subset of well-designed studies of Gulf War veterans that contained analyses of neurologic effects in relation to pesticide or solvent exposures. Tables 7.1 and 7.4 summarize information about each study's population, including exposure to relevant pesticides and solvents, findings, and limitations. The only

[2]*Neurologic effects* is a broad term loosely defined to encompass many of the unexplained symptoms—such as headache, pain, and fatigue reported by Gulf War veterans.

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findings reported in those tables are related to symptom–exposure relationships. The limitations listed are those identified by the study authors or by the committee. The studies are divided into two general types: population-based and military-unit-based.

Population-based studies are methodologically the most robust type of epidemiologic study because they include study subjects representative of a population of interest, which in this case is Gulf War veterans. A cohort may include all personnel from a given country who were deployed to the Persian Gulf (Goss Gilroy Inc., 1998) or a randomly selected sample of those deployed (Unwin et al., 1999). Population-based studies attempt to sample an entire cohort by contacting people where they live, in contrast with studies that include only veterans who seek treatment or who remain in military service (for example, on a particular base or in a particular branch, such as the Air Force). Studies of military units or other military subgroups are less representative of the broader Gulf War veteran population than are population-based studies (IOM, 2000). The largest and most representative population-based study of US Gulf War veterans (Kang et al., 2000) is not included in the body of evidence evaluated by the committee, because the study, by design, examined only symptom or syndrome prevalence, not symptom–exposure relationships.

Most studies of Gulf War veterans were designed to detect the nature and prevalence of veterans' symptoms and illnesses and whether they constituted a new syndrome rather than specifically to assess the effects of exposure to insecticides or solvents. When the effects of exposure to various agents were assessed, numerous potential agents were evaluated in the same study. For example, in one key population-based study (Cherry et al., 2001a), only four of 14 potential exposure categories were related to insecticides or solvents. When insecticide or solvent exposures were assessed, few investigators attempted to quantify exposures to specific agents. Questions asked were very general—for example "Did you handle pesticides?" "Did you bathe in or drink contaminated water?"

Most of the studies were cross-sectional, with outcomes and exposure to various agents measured simultaneously after the Gulf War had ended. Cross-sectional studies limit opportunities to learn about symptom duration and latency of onset (IOM, 2000). They are especially subject to recall bias: veterans who develop symptoms may be more likely than asymptomatic veterans to recall particular exposures. Symptoms reported in cross-sectional studies do not necessarily accurately represent the total symptom experience after an exposure. Many cross-sectional studies of Gulf War veterans were also limited by being conducted years after the war. Only one cohort was studied soon after the war and then longitudinally (Proctor et al., 1998). Furthermore, studies may not have examined outcomes in relation to insecticide and solvent exposures.

The veteran population and sampling strategies used varied widely from study to study. Two studies attempted to include all the Gulf War veterans from a particular country (Goss Gilroy Inc., 1998; Suadicani et al., 1999). Others used a random sample of veterans from a country (Cherry et al., 2001a; Unwin et al., 1999) or from a region of a country (Iowa Persian Gulf Study Group, 1997). Still others used veterans who demobilized at a given base in the country (Proctor et al., 1998) or members of a specific military unit (Gray et al., 1999; Haley and Kurt, 1997). Most studies used active-duty veterans, reserve veterans, or veterans who left military service; but some (Gray et al., 1999; Nisenbaum et al., 2000) used only veterans who had remained in active service for many years after the war. Using only active-duty veterans creates selection bias by potentially excluding those who had suffered the most disabling symptoms and had left the military. One study included mainly veterans who

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had served in the Persian Gulf as peacekeepers after the war; the majority had served many years after hostilities ended (Suadicani et al., 1999).

All Gulf War studies relied on self-reports of insecticide or solvent exposure. In most cases, the self-reports were made years after the end of the war. Most studies did not identify specific insecticides or solvents. Some broke down potential exposure into broad categories (for example, use of personal pesticides, pesticide handling, and spraying of quarters), but others simply asked about exposure to "pesticides" or "solvents." Because the studies all used self-reported data generally gathered years after the events in question, there is a strong possibility of recall bias—that is, veterans with symptoms would be more likely than those without symptoms to recall exposure.

Most of the studies relied on symptom self-reports elicited via questionnaire or structured interview. Several approaches were taken to combine the reported symptoms into outcome variables. One approach was to use a statistical method called factor analysis to uncover an underlying structure in reported symptoms (Cherry et al., 2001a; Fukuda et al., 1998; Haley and Kurt, 1997).[3] A second approach attempted to match symptoms in some way to previously defined syndromes or illnesses (Iowa Persian Gulf Study Group, 1997; Nisenbaum et al., 2000; Unwin et al., 1999). In some cases, previously validated instruments were used. In others, symptoms were assembled into established syndromes on the basis of criteria devised by the investigators; subjects who did not meet established syndromes or diagnoses were said to have unexplained symptoms that could be related to a Gulf War exposure. Other studies did not attempt a synthesis of any sort but searched for associations between exposures to various agents during the Gulf War and individual symptoms.

Another limitation of Gulf War studies was the problem of multiple comparisons between exposure to numerous agents and health outcomes. When investigators examine a large number of exposure–symptom associations, the chances of reporting a spurious association as statistically significant (a type I error) are increased. Gulf War studies took a wide variety of statistical approaches to adjust for the problem of multiple comparisons. However, many did not account for that problem and reported as statistically significant any association with a p value of 0.05 or less. In some of those studies, the investigator did not adjust for multiple comparisons because of the exploratory nature of the study, and their desire to reduce the probability of not finding a true association (a type II error). Other investigators were more conservative and set a more stringent significance level to reduce the probability of a type I error (Cherry et al., 2001a; Haley and Kurt, 1997; White et al., 2001).

Many studies noted that many different agents were associated with the outcomes they measured, but only one attempted to examine the association between specific agents and found them to be strongly correlated (Cherry et al., 2001a), however, the interrelationships might reflect information bias and might be an important limitation of the study.

The limitations described above precluded the committee from drawing specific conclusions solely from studies of Gulf War veterans. The committee therefore combined its evaluation of the evidence from Gulf War studies with the evidence from other populations (mostly in occupational studies). The committee then drew conclusions from the entire body of evidence. That combined approach was undertaken for only two neurologic effects—peripheral neuropathy and neurobehavioral effects—because there were no peer-reviewed

[3]The studies are not reported in Table 7.1 if they did not address symptom–exposure relationships.

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published studies of Gulf War veterans for other neurologic effects covered in this chapter. (The committee did not evaluate a study of amyotrophic lateral sclerosis, because it has not yet been peer-reviewed or published.)

INSECTICIDES AND PERIPHERAL NEUROPATHY

Peripheral neuropathy is a general term referring to any abnormality, inflammation, or disease of a peripheral nerve. The most common causes of peripheral neuropathy are diabetes and alcoholism (Poncelet, 1998). The symptoms of peripheral neuropathy include numbness, tingling, and weakness, but the nature and pattern of symptoms can vary greatly, depending on the etiology.

With the exception of the Gulf War veteran studies, the committee defined peripheral neuropathy, for purposes of its evaluation, as requiring a diagnosis by a thorough neurologic examination and confirmatory findings from quantitative laboratory tests, such as nerve-conduction studies and electromyography (see Appendix F).

The question posed is whether peripheral neuropathy is associated with exposure to the insecticides and solvents of interest to the committee. In the subsection below, the committee evaluates the body of evidence from studies of Gulf War veterans and from occupational studies of exposure to OP insecticides and relevant solvents (those identified as having been present in the Persian Gulf).

Gulf War Veterans and Peripheral Neuropathy

Three studies of Gulf War veterans assessed the relationship between insecticide or solvent exposures in the Persian Gulf and peripheral neuropathy (Table 7.1). The general limitations of Gulf War studies have been described in the previous section, and a description of the entire body of Gulf War studies, regardless of whether they examine insecticide or solvent exposure, is in Appendix A.

Each of the studies evaluated in this section, like most Gulf War studies, used questionnaires to assess exposure to various agents and symptoms. Peripheral neuropathy was defined in the studies in various ways through symptom reporting, but few included a neurologic examination or confirmatory electrophysiologic tests.

In the Gulf War studies, peripheral neuropathy and symptoms suggesting peripheral neuropathy were typically among a broad array of outcomes examined. Likewise, insecticide or solvent exposure was among a host of agents being examined. None of the studies of Gulf War veterans, however, focused exclusively on the question of whether insecticide or solvent exposure in the Persian Gulf was associated with the development of peripheral neuropathy.

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TABLE 7.1 Gulf War Studies and Peripheral Neuropathy

Reference	Population	Self-Reported Exposure to Relevant Pesticides or Solvents	Health Outcome or Test Type	Results	Limitations
Military-Unit-Based Studies					
Haley & Kurt, 1997 US	249 deployed veterans from Navy reserve battalion (Seabees); Nested case–control study of 23 veterans with up to three newly defined syndromes (derived from factor analysis) vs 229 veterans without newly defined syndromes	Five of 18 related to pesticides or solvents: "DEET-containing insect repellent," "environmental pesticides," "pesticides in uniforms," "pesticides in flea collars," "CARC paint on vehicles"	Symptom questionnaire Exposure questionnaire	Amount of insect repellent (DEET) applied to skin was associated with arthro-myo-neuropathy syndrome (RR = 1.6, 95% CI = 0.5–5.5 for lowest exposure; and RR = 7.8, 95% CI = 2.4–24.7 for greatest exposure); association held only for veterans using government-issued insect repellent, not commercial insect repellent.	Self-reported symptoms and exposure to various agents; lack of neurologic examination and electrophysiologic testing; small sample size; low participation rate
				In a separate clinical study (Haley et al., 1997b), subset of five veterans with arthro-myoneuropathy syndrome was evaluated by blinded neurologists, who concluded that clinical and electrophysiologic findings were insufficient to diagnose any known syndrome	Lack of control group in original cohort; limited representation of entire Gulf War cohort
Proctor et al., 1998 US	300 US deployed veterans from Massachusetts (Fort Devens) and New Orleans vs 48 Germany-deployed veterans	One of eight environmental exposures related to pesticides or solvents: "pesticides"	Symptom questionnaires; Exposure questionnaires (Clinical evaluations used for other end points but not for peripheral neuropathy)	Exposure to "pesticides" associated with neurologic symptom group (headache, numbness in arms or legs, dizziness) ($p = 0.007$), musculoskeletal symptom group ($p = 0.001$) "Pesticide" exposure not significantly related to neuropsychologic symptom group (difficulty in learning and concentrating, confusion) or psychologic symptom group (inability to fall asleep, anxiety, depression)	Self-reported symptoms and exposure to various agents; moderate to low response rate; limited representation of entire Gulf War cohort

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Reference	Population	Self-Reported Exposure to Relevant Pesticides or Solvents	Health Outcome or Test Type	Results	Limitations
Population-Based Study					
Cherry et al., 2001a UK	4795 UK veterans deployed to Gulf War (and validation cohort of 4750) vs 4793 UK veterans not deployed to Gulf War	Four of 14 related to pesticides or solvents: "using insect repellent on the skin," "handling of pesticides," "quarters sprayed with insecticides," and "respraying of vehicle"	Symptom questionnaire, which directly asked about symptoms but also contained two mannequin diagrams for shading areas indicating numbness and tingling to indicate peripheral neuropathy; Exposure questionnaire; Surveys completed 7 or more years after war	Handling of pesticides was associated with "peripheral symptom factor;" using insect repellent was associated with "peripheral symptom factor" in dose-dependent manner; handling of pesticides was associated with peripheral neuropathy, indicated by shading areas of numbness and tingling on two mannequin diagrams (OR = 1.26, $p < 0.001$)	Self-reported symptoms and exposure to various agents; lack of neurologic examination and electrophysiologic testing

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Cherry and colleagues (2001b) conducted the only population-based study that included assessment of peripheral neuropathy. They collected symptom and exposure data from UK veterans 7 years or more after the Gulf War. The veterans in this study consisted of two random samples of all UK troops deployed to the Gulf War stratified by age, sex, and rank. One sample was designated the main cohort ($n = 4795$), the second a validation cohort ($n = 4793$). (The cohorts did not overlap with the UK cohort studied by Unwin and colleagues [1999].) A questionnaire was used to gather data on 95 symptoms on visual analogue scales. The questionnaire also included diagrams of two mannequins on which respondents were asked to shade areas where they were experiencing pain or numbness and tingling. A second questionnaire, completed concurrently, asked for the dates when the respondent had been sent to each location in the Persian Gulf and the types of exposures experienced there. Four of 14 exposure categories were insecticide- or solvent-related: "using insect repellent on the skin," "handling of pesticides," "quarters sprayed with insecticides," and "respraying of vehicles." Multiple regression—controlling for officer status; service in army, navy, or air force; current service status; age; sex; and marital status—was used to determine the relationship between self-reported exposure and seven symptom factors extracted by factor analysis from the symptom questionnaire. Analyses were carried out separately for the two cohorts, and results were reported only when they reached a significance level of 0.001 in the combined cohorts and 0.01 in each of the two cohorts.

Through symptom reporting, the investigators defined *peripheral neuropathy* in two ways: a "peripheral" symptom factor (one of the seven symptom factors), which included such symptoms as painful tingling or loss of sensation in hands and feet, feeling stiff, muscle cramps, tingling under the skin, cold hands and feet, watery eyes, acne and rashes, and itchy skin; and areas of numbness or tingling that veterans shaded on the pictures of mannequins (Cherry et al., 2001b).

Pesticide handling and using insect repellent were associated with the peripheral symptom factor. Trends in the dose-response relationship were explored by relating days of exposure to the symptom score. There was a clear dose-response trend across three of the four exposure categories for insect-repellent use; however, the trend was less apparent for handling of pesticides, although those exposed for more than 63 days had higher symptom scores than those exposed for shorter periods.

Veterans' shading of areas of numbness and tingling on the mannequin diagrams was not included in the factor analysis but was analyzed separately. In a logistic-regression analysis that controlled for other types of exposures, pesticide handling (but not using insect repellent) was associated with shading on the mannequins. There was a dose-response gradient. Almost 35% of Gulf War veterans who reported handling pesticides for more than a month indicated numbness or tingling on the mannequin diagrams, compared with 13.6% of veterans who did not report handling pesticides. This study was well designed and reveals a dose-response relationship, but it is limited by potential recall bias and lack of clinical evaluations or nerve-conduction studies.

Haley and Kurt (1997) examined pesticide, solvent, and other agents in relation to three of six new syndromes[4] that they had defined by factor analysis in a companion publication (Haley et al., 1997a). Their hypothesis was that the new syndromes were related

[4]Numerous other factor analyses of more-representative populations have not supported the existence of a new syndrome (see Appendix A).

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to exposure to OP insecticides and other cholinesterase-inhibiting insecticides used in the Gulf War. Veterans in the study were members of a single naval reserve construction battalion (Seabees) known to have a high prevalence of postwar illness. Efforts were made to include veterans who had left the service and those still serving; a total of 249 veterans (41% of 606 battalion members) participated. An exposure questionnaire contained five of 18 exposures that were relevant to the committee's mandate: "DEET-containing insect repellent," "environmental pesticides," "pesticides in uniforms," "pesticides in flea collars," and "CARC (Chemical Agent Resistant Coating) paint on vehicles." When veterans reported exposure to any agent, additional questions were asked to address such issues as the duration and dose of exposure and the anatomic areas exposed. For insect-repellent use, the questionnaire addressed the brand of insect repellent, typical frequency of repellent application, and the amount typically applied each time; this allowed the authors to construct a six-point scale to quantify the exposure.

A complex approach was used to address clusters of symptoms experienced by the veterans. A survey booklet was used to elicit reports of the major symptoms commonly associated with the Gulf War on the basis of reporting to Department of Defense (DOD) and Department of Veterans Affairs (VA) registries (see Appendix A). The booklet directed veterans who responded affirmatively to one of the symptoms, to answer an additional set of four to 20 followup questions designed to differentiate characteristics of the symptom. A two-stage factor analysis was used to develop symptom scales from each set of followup items and then to organize the symptom scales into six factors. Six "syndromes" were defined from the factors by dichotomizing each factor and using a cutoff designed to label at least nine veterans as "cases" for each syndrome (Haley et al., 1997a). Logistic regression was then used to explore possible associations between agents each of the six syndromes (Haley and Kurt, 1997).

Syndrome 3 (labeled "arthro-myo-neuropathy" by the investigators) was the only one of the six to include peripheral neuropathy-like symptoms, including joint pains in hips and extremities or neck and shoulders; generalized muscle weakness; fatigue; myalgia in arms, neck, shoulders, legs, buttocks, or back; and tingling in the extremities. This syndrome was associated with the use of DEET-containing insect repellent. A dose-response trend was found ($p < 0.001$); the syndrome was more prevalent in those who used greater amounts of repellent or used it more frequently (relative risk [RR] = 1.6–7.8 with increasing reported use; Table 7.1). In a multiple logistic regression, the association held only in veterans who used government-issued repellent (adjusted odds ratio [OR] 1.54; confidence interval [CI] 95%, = 1.17–2.03), but not in those using personally acquired brand-name repellent OFF! (adjusted OR = 1.08, 95% CI = 0.79–1.46) or Skin-So-Soft (adjusted OR = 0.87, 95% CI = 0.64–1.18).[5] No associations were found between syndrome 3 and three other pesticide exposures—environmental pesticides, pesticides in uniforms, and pesticides in flea collars—or the single solvent exposure CARC paint on vehicles. The significance level was set at 0.005 because of the large number of comparisons. The authors provided a detailed discussion of possible biologic mechanisms to support the association of syndrome 3 with the use of DEET but did not provide any explanation of the lack of association with other pesticide exposure.

[5] Haley and Kurt (1997) report that most government-issued insect repellent contained 33% DEET, but some contained 75% DEET; Off! contained 31% or less DEET, and Skin-So-Soft contains no DEET.

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In a later study (Haley et al., 1997b), the investigators identified the 23 veterans who had the highest scores for syndromes 1–3. The 23 veterans were matched by age, sex, and educational level with 10 controls selected from 70 veterans who had been deployed to the Persian Gulf and had reported no serious health problems. An additional 10 matched controls were selected from veterans who had not been deployed to the Persian Gulf. Cases and controls were invited for further investigations that included a clinical neurologic examination. Five subjects received nerve-conduction studies after "initial review of the study results that suggested the presence of peripheral neuropathy." Six neurologists, blinded to case or control status, reviewed all clinical findings and attempted to arrive at a consensus diagnosis. The relationship to insecticide or solvent exposures was not addressed in the report of this study. Of the 22 veterans identified in the initial study as suffering from syndrome 3, only five were included in this followup clinical study. Three of the five had at least one abnormality on neurologic examination (a similar proportion of controls had at least one abnormality). Only three of the syndrome 3 veterans had nerve-conduction studies; all three had abnormal tests of cool and vibratory sensation in the upper or lower extremities, and two had borderline abnormal motor-nerve conduction velocity in the lower extremities. The blinded neurologists concluded that the findings were nonspecific and insufficient to diagnose any known syndrome in any subgroup of subjects.

Proctor and colleagues (1998) tested the hypothesis that symptoms in Gulf War veterans were related to a number of specific agents, including exposure to pesticides, by using a random sample of two cohorts of US veterans who were identified at the time of demobilization immediately after the Gulf War. One of the cohorts was from Massachusetts (Fort Devens), the other from New Orleans. The two cohorts were compared with veterans deployed to Germany during the same era. The sample was stratified to oversample women and to give equal representation to veterans who had reported higher and lower prevalence of symptoms in prior surveys. Exposure to various agents during the Gulf War were assessed with a questionnaire that addressed eight exposures on a scale of 0–2 (0 = no exposure; 1 = exposed; 2 = exposed and felt sick at the time). None of the questions addressed relevant solvent exposures. One question addressed exposure to "pesticides."

Symptoms were reported on a 52-item checklist, from which the analysis grouped three or four related symptoms into nine symptom groups referring to body systems. Four judges who specialized in neuropsychology, and environmental and occupational health made the assignment of symptoms to a particular group independently. Two of the symptom groups bore some resemblance to symptoms of peripheral neuropathy. The neurologic group incorporated three symptoms: headache, numbness in arms or legs, and dizziness or lightheadedness. The musculoskeletal group also incorporated three symptoms: joint pains, backache, and neck ache or stiffness.

A series of multiple regressions explored associations between self-reported exposure to various agents and symptoms related to symptom groups. The analysis controlled for age, sex, education, the presence of anxiety disorder, posttraumatic stress disorder (PTSD), and the score on a 34-item expanded combat-exposure scale (designed to assess the presence and frequency of a variety of prominent war-zone stressors). Standardized regression coefficients and p values were reported for all associations reaching $p < 0.05$. According to that significance criterion, exposure to pesticides was associated with the neurologic symptom group ($p = 0.007$) and the musculoskeletal symptom group ($p = 0.001$). Pesticide exposure was not related to the neuropsychologic symptom group

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(difficulties in learning new material, difficulty in concentrating, and confusion) or the psychologic symptom group (depression and frequent periods of anxiety or nervousness). Correction for depression scores did not change the associations.

Summary and Conclusion

Most of the Gulf War studies of peripheral neuropathy-like symptom–exposure relationships did not conduct clinical examinations or nerve-conduction studies. Instead, studies relied on analysis of symptom self-reports. Therefore, it is not clear that veterans identified with some type of symptom-defined peripheral neuropathy actually had clinically diagnosable peripheral neuropathy, as defined by the committee.

The results of the studies were mixed. In one large, representative sample of UK veterans (Cherry et al., 2001a), associations were found between Gulf War pesticide exposure and self-reports of neuropathy-like symptoms. A study (Haley and Kurt, 1997) of a single US military unit-identified symptom cluster (labeled syndrome 3 by the investigators) found associations with government-issued insect repellent but not with brand-name repellents; moreover, a panel of six neurologists who examined a subset of five syndrome 3 subjects was unable to arrive at any neurologic diagnosis. In another study (Proctor et al., 1998), the investigators created groups of symptoms from responses to questionnaires. Their musculoskeletal and neurologic symptom groups, which were defined as having some peripheral neuropathy-like symptoms, were both associated with self-reported exposure to "pesticides," but there was no more specificity about the type of pesticide or the degree of exposure. None of the studies found a relationship between *solvent* exposures and peripheral neuropathy, but very few asked about solvent exposures on the exposure questionnaire.

The committee was unable to draw particular conclusions from these studies, because of their limitations, both study-specific and more general. The committee did combine findings from the Gulf War veterans' studies with those from other populations as they drew conclusions from the entire body of evidence.

OP Insecticides and Peripheral Neuropathy

Over 30 years ago, researchers began to report subtle yet persistent effects on the PNS from OP compounds (Roberts, 1976). This subtle type of peripheral neuropathy is pathologically and behaviorally distinct from organophosphate-induced delayed neuropathy (OPIDN), a more serious and disabling syndrome caused by high exposure to some OP compounds (Chapter 3).

Case reports, case series, and animal studies have been used to conclude that high dose exposure to OP insecticides may result in OPIDN through an irreversible inhibition of the enzyme NTE (Chapter 3). The committee did not examine studies of OPIDN as an end point after OP insecticide exposure because the human evidentiary base consists only of case studies and case series and because OPIDN is pathologically and behaviorally distinct from the more subtle type of peripheral nephropathy that is addressed in controlled studies of Gulf War veterans and occupational studies. As background, it is important to note that only two of the OP insecticides considered in this report, chlorpyrifos and dichlorvos, inhibit NTE—yet only at doses that are sufficient to cause lethal cholinergic poisoning. There were no reports of poisoning in military personnel in the Gulf War.

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As noted earlier, the committee defined peripheral neuropathy, for purposes of evaluation, as requiring a diagnosis by a thorough neurologic examination and confirmatory findings from quantitative laboratory testing. For confirmatory neurophysiologic testing, the committee favored nerve-conduction studies and electromyography (Appendix F). The committee viewed vibrotactile testing by itself as too limited a neurophysiologic measure to confirm the diagnosis of peripheral neuropathy. The committee excluded studies that did not have careful neurologic examinations.

Postural sway, which could be an indication of either a PNS or a CNS effect, is reported in this section because of its inclusion in several studies of peripheral neuropathy. Some of the studies on peripheral neuropathy evaluated here are also evaluated in the section on neurobehavioral effects because they contained measures of both neurologic outcomes.

Limitations of Studies of Peripheral Neuropathy

The major limitations of peripheral neuropathy studies include exposure to many types of pesticides or solvents and poor documentation of specific exposure. Other problems are misclassification of measurement and confounding.

Misclassification of measurement can occur with neurophysiologic testing to support the diagnosis of peripheral neuropathy. Nerve conduction can be slowed by the ambient temperature and by the height of the person. It is important to consider those variables in the interpretation of results. For the most part, it is less likely that test conditions and height will differ according to exposure group (such as exposed vs nonexposed). It is more likely that inattention to those variables would result in an underestimation of associations between outcome and exposure. Such diseases as diabetes and hypothyroidism, and alcohol use and nutritional deficiency can cause peripheral neuropathy, so it is important to assess their prevalence in the exposure groups; if the prevalence is different between groups, the difference must be taken into account in the analysis.

Confounders are factors that are related to both outcome and exposure. These extraneous variables may be true risk factors for the outcome but differ in distribution between exposure groups. For example, age is often a confounder because it is a risk factor for a number of diseases and may be associated with exposure. If not considered in the analysis, observed differences in likelihood of the outcome between two exposure groups may be attributed in whole or in part to the difference in age distribution between exposure groups. Confounding may be addressed in study design through restriction or matching or be adjusted for in the analysis. It is important to note that inadequate control for confounding variables can result in overestimation or underestimation of effect.

Another confounder, particularly in cross-sectional studies of long-term effects, is the inclusion of workers with current exposure. What is reported as a long-term effect may in fact be a short-term effect of current (or recent) exposure. That is less of a problem for peripheral neuropathy than for neurobehavioral effects. Peripheral neuropathy, based on clinical examination and confirmed by electrophysiologic alterations (such as decreased conduction velocity or pathologic evidence of denervation), usually takes several weeks to develop, can be tested objectively, and generally is not totally reversible when exposure to the agent is removed (Aminoff, 1987). Neurobehavioral effects, in contrast, may or may not persist once exposure ceases. The committee considers peripheral neuropathy to be a long-term effect that persists for months or years.

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Epidemiologic Studies of Exposure to Insecticides

The body of epidemiologic evidence of an association between OP insecticides and peripheral neuropathy consists of numerous studies, but most were found by the committee to have methodologic limitations, as discussed below and in Table 7.2. The committee excluded several studies from consideration because of design flaws or lack of a thorough clinical examination for the diagnosis of peripheral neuropathy (Ames et al., 1995; Engel et al., 1998; London et al., 1998; Steenland et al., 1994). In two of the studies, the clinical examination was used only to exclude other causes of peripheral neuropathy rather than to diagnose it (Ames et al., 1995; Steenland et al., 1994); these studies were nevertheless evaluated in the next section, on neurobehavioral effects, because their methods were stronger for that set of outcomes. Two of the best-designed studies (Savage et al., 1988; Steenland et al., 2000) evaluated by the committee did not find evidence of peripheral neuropathy.

The committee reports its findings in one section combining studies of OP-exposed people with and without a history of OP poisoning. The reason for combining them is that, findings of both types of studies are negative. The combination approach contrasts with the next section, on neurobehavioral effects, in which the committee separates studies of previously poisoned people with those who have been exposed to pesticides but were not poisoned.

Savage and colleagues (1988) studied a group of 100 agricultural workers in Colorado and Texas with documented past OP poisoning (from rosters of documented pesticide poisoning in Colorado and Texas) and 100 matched controls. The last poisoning occurred an average of 9 years before testing, but there is no information about the extent of chronic OP exposure after the poisoning. The study excluded workers reporting exposure within 3 months of evaluation, so recent exposure cannot account for effects. Because most of the testing was with a comprehensive neurobehavioral battery, the study is described more extensively in a later section. The clinical neurologic examination consisted of 50 separate tests, including tests of cranial nerve function, motor-system function, and sensory-system function. The only difference between poisoned and nonpoisoned groups was an abnormality on one of 23 motor-reflex tests in the poisoned group.

Steenland and colleagues (2000) studied 191 former or current termiticide applicators exposed primarily to chlorpyrifos. Since the banning of chlordane in 1988, chlorpyrifos has been the main termiticide used. The mean time of exposure was 2.4 years for chlorpyrifos and 2.5 years for chlordane. Two-thirds of the exposed group were current applicators in a 12-county area of North Carolina. The study was population-based, using a list of all pesticide control applicators in North Carolina; of 688 licensed operators with more than 1 year of exposure, investigators were able to contact 200 for study.

For exposure assessment, questionnaire response and job history were supplemented with measurements of a urinary metabolite of chlorpyrifos (34% had very recent exposure). Eight applicators had been previously poisoned, according to self-reports. The exposed group was compared with a nonexposed group of 189 people (106 friends of exposed subjects and 83 state blue-collar municipal workers). Both the exposed subjects (36%) and the comparison group (up to 52%) also had a history of occupational solvent exposure.

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TABLE 7.2 Peripheral Neuropathy and Organophosphorous Insecticide Exposures

Reference	Population	Insecticide	Health Outcome or Test Type	Adjustment	Results	Limitations
Savage et al., 1988	100 OP-poisoned workers (Colorado, Texas registries, 1950–1976) vs 100 nonpoisoned workers 7–11 years after last OP poisoning	OPs; methyl parathion, parathion account for 96 of 100 OP poisonings	Neurologic examination, 50 tests	Pair matching on age, sex, level of education, social class, occupational class, ethnic background (Hispanic)	No difference on neurologic exam except for one test of motor reflex; motor summary score nonsignificant	
Steenland et al., 2000	191 termiticide applicators from North Carolina registry (including 105 current applicators and eight formerly poisoned) vs 189 nonexposed controls (106 friends of exposed and 83 state employees); Median 1.8 years of exposure (1987–1997)	Chlorpyrifos, some chlordane (1987–1988)	Neurologic examination; nerve-conduction velocity; vibrotactile sensitivity of finger, toe via automated device; postural sway; arm, hand tremor via device	Regression: age, race, education, current smoking, body-mass index	Nerve-conduction velocity, tremor, vibration sensitivity nonsignificant; worse performance on postural sway	Possible selection bias due to inability to locate majority of exposed population; occupational solvent exposure a potential confounder for exposed, controls
Jamal et al., 2001	16 OP-poisoned sheep dippers in UK vs 16 sheep dippers with chronic low OP exposure and 16 controls; exposed for 4 years or more; 4 months since last exposure	Diazinon, propetamphos, clorfenvinphos	Clinical examination (scores for symptoms, tendon reflexes); nerve-conduction studies; needle EMG; thermal threshold; vibration threshold; central evoked potentials	Controls matched for age, sex	Significant differences between all groups in all end points except central evoked potentials; OP-poisoned performed significantly worse than OP chronic low-level, which performed worse than controls; increases in vibration, cold threshold	Selection bias in two exposed groups

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Reference	Population	Insecticide	Health Outcome or Test Type	Adjustment	Results	Limitations
Stokes et al., 1995	90 male pesticide applicators vs 68 population-based controls; New York state; 20 years of exposure	Azinphos-methyl (mean, 14 years), chlorpyrifos (mean, 4 years), diazinon (mean, 1 year)	Vibration sensitivity (Vibratron II); clinical examination, detailed electrophysiologic studies in subset (n = 9) with over 20 years of exposure (Horowitz et al., 1999)	Controls matched for sex, age, county of residence, but not height; controlled for recent exposure by testing during off-season	Vibration threshold higher in dominant, nondominant hands of pesticide applicators, but not in feet; scores for vibration threshold higher among applicators; in four of nine subjects with over 20 years of exposure, reduced sensation in lower extremities or slowed F-wave latency (Horowitz et al., 1999)	Low response rate (90 of 554); no indication of blinded testing
Amr, 1999	300 pesticide applicators vs 300 community controls; Egypt	OPs (including malathion, dichlorvos); pyrethroids (type 1: sumithrin, d-allethrin; type 2: cypermethrin, deltamethrin, tetramethrin); carbamate (propoxpur)	Clinical examination, EMG, EEG	Controls matched for age, education, socioeconomic status	Sensory hypoesthesia; muscle weakness; static tremor; abnormal deep-tendon reflexes; EMG not significant; EEG significantly higher frequency	Sparse on methods
Otto et al., 1990	229 pesticide workers vs 180 fertilizer workers exposed to lead, sulfuric acid and 167 textile workers; 1–26 years of exposure for most pesticide workers (range, 1–46 years); Egypt	OPs (including diazinon, malathion)	Neurologic examination, vibration threshold of index finger of nondominant hand via Optacon voltage	Controlled for age, education, but not alcohol consumption	Bilateral involuntary tremors on examination in pesticide, fertilizer workers (1985–1986); bilateral abnormal vibration sensitivity on examination in pesticide fertilizer workers (1985–1986); increased vibration threshold in pesticide workers	Automated tremor device not used; vibration device used to test only fingers, not toes

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Reference	Population	Insecticide	Health Outcome or Test Type	Adjustment	Results	Limitations
Cole et al., 1998	144 pesticide applicators vs 30 nonexposed farm workers and 72 nonexposed local controls; 9–17 years of past and current exposure; 28% of applicators report past OP or carbamate poisoning; Ecuador	OP (metamidophos); carbamate insecticides; dithiocarbamate fungicides	Neurologic examination; symptom questionnaire; vibration threshold	Controls matched for age, sex, level of education	Applicators report more peripheral nerve symptoms, more signs of poor coordination, reduced power, abnormal deep-tendon reflexes; applicators had significantly higher vibration thresholds in toe	No nerve-conduction velocity; EMG testing; mixed nature of insecticide exposures

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Testing included clinical examination, vibration sensitivity, tremor (through an automated device), nerve-conduction studies (peroneal, sural, and ulnar nerves), neurobehavioral batteries, and postural sway using platform posturography. There were no differences between exposed and nonexposed groups on clinical neurologic examination. Among the few abnormal findings were that exposed subjects had lower ulnar amplitudes than did the 83 state employees. There was no significant association between the presence of a susceptible genotype (paraoxonase polymorphism) and a history of poisoning (Chapter 3). Currently exposed workers had significantly lower ulnar nerve amplitudes, but they also had higher sural nerve conduction velocities. There was no relationship between nerve-conduction findings and duration of exposure. In other tests of peripheral neuropathy, there was no association between exposure and tremor or vibration sensitivity. The exposed group had greater length of sway on some of the 12 tests of postural sway, which were conducted under various conditions with eyes open and eyes closed. The abnormal sway findings were not associated with urinary OP metabolite concentrations.

The major strength of the study was that it was population-based. Its major limitation was possible selection bias due to inability to locate the majority of the exposed target population. The nature of the selection bias, however, was unclear. Workers more affected by exposure to insecticides may have been more likely to participate, or those more affected may have been harder to find. Another limitation was the history of occupational solvent exposure among exposed and controls.

Jamal and colleagues (2001) performed a small study with the most detailed clinical and neurophysiologic assessment of peripheral neuropathy. The goal was to compare the pattern of deficits occurring in sheep dippers of the UK who had previous OP poisoning with sheep dippers who had chronic, lower OP exposure and no history of poisoning. Sheep farmers in the UK were, until recent years, required to periodically dip their flocks in OP insecticides for sheep scab and other parasites. The two groups of exposed farmers (16 per group) were compared with age- and sex-matched subjects (16, mostly office workers) who had not been exposed to OP insecticides. Both exposed groups had been exposed for at least 4 years and had not been exposed within 4 months of the study.

The identification of farmers with past OP poisoning and those with chronic exposure was done by two methods, which may have introduced different types of selection bias. Those with OP poisoning were chosen at random from a list of 200 sheep farmers compiled by a voluntary organization. The list consisted of people who claimed to have developed chronic neurologic problems after their poisoning. That might have led to an overrepresentation of exposed subjects with the outcome of interest. The OP farmers with chronic exposure, but no poisoning, were selected at random from a telephone directory listing of almost 2000 farms in a 16-mile radius of Glasgow, Scotland. They recalled no history of symptoms or acute poisoning. That method is less likely to introduce selection bias, but there were difficulties during the recruitment phase and screening process during which the 39 sheep farmers identified were reduced to a total of 16. The investigators did not state their methods of exclusion of all other causes of peripheral neuropathy and did not take an exposure history. Even though the investigators found peripheral neuropathy by using detailed clinical and electrophysiologic measures, the results are compromised by selection bias in the exposed cohorts.

Stokes and colleagues (1995) studied 90 male pesticide applicators identified through a New York state registry and compared them with 68 population-based controls.

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The mean duration of OP exposure was 20 years. Testing during the offseason precluded detection of short-term effects. The authors found vibration threshold to be higher in the dominant and nondominant hands of pesticide applicators but not in their feet. The finding of no significant differences in foot-vibration thresholds may be attributable to lack of control for height. One weakness of the study was the lack of peripheral-neuropathy tests beyond vibration thresholds for nonpoisoned subjects. Another weakness of the study was the low response rate (90 of 554 licensed applicators), but this may have biased the findings in either direction. A followup study of nine of the subjects with increased vibration threshold and more than 20 years of exposure found reduced sensation in lower extremities or slowed F-wave latency (Appendix F), but there was no comparison group (Horowitz et al., 1999).

A study in Ecuador by Cole and colleagues (1998) examined peripheral nerve function in 144 pesticide applicators exposed for 9–17 years to a combination of OPs and carbamates (insecticides and fungicides). The applicators also had current exposure, as evidenced by their occupation and by slightly decreased red-cell AChE. Some 28% of the applicators had at least one past poisoning. The subjects were compared with two groups of controls (farm workers and nonfarm workers, such as housewives, students, and laborers) matched for age, sex, and education. Pesticide exposures among applicators were estimated from farm records and interviews concerning their total years of past and current use. Many applicators had engaged in practices likely to increase exposure, such as mixing pesticides with hands and a stick, using leaking backpack sprayers, and using little personal protective equipment. All subjects and controls completed a neurologic-symptom questionnaire and had clinical neurologic examinations. Vibration sensation was measured with the Vibratron II device (Appendix F).

The applicators reported significantly more peripheral nerve symptoms, had more signs of poor coordination, and were significantly more likely to have abnormal deep-tendon reflexes and reduced muscle power. Vibration thresholds in the toe were significantly higher among applicators and among those reporting previous pesticide poisoning (by OP compounds or carbamates). The researchers did not perform nerve-conduction velocity tests or EMG to confirm clinical findings. Another limitation was the mixed nature of the pesticide exposures, including fungicides (which are not being examined in this report). The symptom findings were excluded from the committee's consideration in that they could represent short-term, rather than long-term, effects.

Amr (1999) reported on 300 male pesticide formulators (age, 20–55 years) randomly selected from two pesticide-formulating plants in Egypt. The workers were exposed to a combination of pesticides, including OP compounds (such as malathion and dichlorvos), carbamates (propoxpur), pyrethroids, and DDT. Exposure duration was 5–25 years (mean, 13.9 years). All pesticides formulated by the workers were detectable in air samples at 2–5 times the permissible exposure limits. None of the workers reported prior OP poisoning, but there was no attempt at verification with medical records. The exposed workers were compared with 300 community subjects (nonexposed) who had no history of occupational exposure to pesticides and were matched for age, sex, educational level, and socioeconomic status. Tests included blood-chemistry profiles, electroencephalography (EEG), and EMG (of the anterior tibial and flexor digiti minimi muscles); and the subjects had clinical examinations. Testing of the formulators revealed increases in clinical symptoms and signs of peripheral neuropathy, including sensory hypoesthesia, muscle weakness, static tremor,

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and abnormal deep-tendon reflexes. (The findings are from both pesticide formulators and applicators, without clear identification of occupational group.) The neurologic findings were more prominent in older workers with longer duration of exposure (over 20 years). EEG studies showed that exposed workers had significantly higher frequencies than nonexposed; this is of unknown clinical significance. EMG findings were not significantly different. However, studies were missing crucial information with which to interpret the results. Studies did not report whether the testers were blinded, the selection criteria for subject inclusion or exclusion, and specific test equipment and methods of EMG and EEG analysis. AChE activity, which was assayed at only one of the plants (n = 159), was decreased in about 70% of workers and was about 60–65% lower in them than in community subjects. That indicates recent OP or carbamate exposure. It was unclear whether cholinesterase activity was measured in plasma, red cells, or both.

Otto and colleagues (1990) conducted a study of 229 Egyptian production workers at a pesticide-formulation plant. The study was of current workers (who had significantly reduced serum cholinesterase). Neurologic examinations were performed 2 years in a row (1985–1986). The committee evaluated only study findings regarding peripheral neuropathy; it excluded study findings regarding neurobehavioral effects because the study was of current workers who had both current and past exposure (such findings may reflect short-term rather than long-term effects, whereas peripheral neuropathy is more likely a long-term effect). For neurologic examinations, workers were compared with 180 fertilizer workers exposed to other neurotoxicants but not to OP compounds. Neurologic findings from a separate comparison group of textile workers were not used in the analysis, because the clinician performing the examination was not blinded to exposure status. When age and education were controlled for, bilateral involuntary tremors and increased vibration threshold were found on examination in 1985 and 1986. An automated tremor device was not used, and the vibration device was used to test only fingers, not toes. The findings applied to both pesticide and fertilizer workers. About half the pesticide workers had 12-46 years of employment at the plant, and a slightly higher percentage of fertilizer workers had similarly long employment. However, there is scanty information about the nature of job exposure. There was also no measurement of nerve-conduction velocity.

Summary and Conclusion

The two stronger studies covered in this section did not find peripheral neuropathy associated with occupational exposure to OP insecticides (Savage et al., 1988 and Steenland et al., 2000). The other studies of peripheral neuropathy evaluated here had some positive findings, but all had design limitations that weakened the validity of their findings.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the organophosphorous insecticides under review and peripheral neuropathy.

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SOLVENTS AND PERIPHERAL NEUROPATHY

It is well established that some solvents that were not sent to the Gulf War—*n*-hexane (found in glues), carbon disulfide, and methyl *n*-butylketone—cause peripheral neuropathy (Graham et al., 1995). With subchronic or chronic exposures to these solvents, symptoms appear insidiously over weeks or months. The clinical features include sensory loss, distal weakness, and areflexia with motor-nerve conduction slowing. Nerve biopsy shows axonal degeneration with axonal swelling. Symptoms can progress for months after termination of exposure (Huang et al., 1989). In mild cases, symptoms eventually resolve; in more severe cases, residual disability persists for a long time (Arlien-Søborg, 1992; Feldman, 1999). On the basis of onset and clinical course, peripheral neuropathy caused by solvent exposure (or, as discussed earlier, by insecticide exposure) is a long-term effect.

Peripheral neuropathy caused by the three solvents mentioned above was initially recognized in humans exposed in the occupational setting and later verified in experimental animals. *N*-hexane and methyl *n*-butyl ketone were found to be neurotoxic after bioactivation to a common toxic metabolite, 2,5-hexanedione. In contrast, carbon disulfide does not require bioactivation. The three solvents produce identical pathologic and clinical changes. Whether solvents sent to the Gulf War are associated with peripheral neuropathy remains controversial. Stoddard solvent, one of the solvents sent to the Gulf War, has some formulations with *n*-hexane, but the concentration is not expected to pose a risk of peripheral neuropathy. Peripheral neuropathy has not been observed in experimental animals exposed to Stoddard solvent (Pryor and Rebert, 1992).

Epidemiologic Studies of Exposure to Solvents

The committee evaluated five studies (Table 7.3) to address the relationship between relevant solvents and peripheral neuropathy (Buiatti et al., 1978; Fagius and Gronqvist, 1978; Gregersen et al., 1984; Mutti et al., 1982; Nasterlack et al., 1999). The studies included workers in the steel industry (Fagius and Gronqvist, 1978), shoe and leather workers (Buiatti et al., 1978; Mutti et al., 1982), painters (Nasterlack et al., 1999), and workers in a variety of jobs with solvent exposure (Gregersen et al., 1984).

Exposure-assessment methods were variable and focused mostly on current exposure, with years of work at the current job used as a proxy for past exposure. The studies used various outcome measures, but all incorporated a clinical examination. Several studies added symptom questionnaires to the clinical examination. Four included nerve-conduction velocity, one used EMG, and two used vibration-perception threshold.

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TABLE 7.3 Peripheral Neuropathy and Solvent Exposure

Reference	Exposed Population	Nonexposed Population	Health Outcomes or Test Type	Solvent	Adjustment	Results	Limitations
Buiatti et al., 1978 Italy	Italian shoe leather workers, perhaps 340; exclusion of workers with history of contact with neurotoxic compounds other than solvents [*n* not given]	"Normal subjects examined in the neurological department during neurological screening of the normal population" [*n* not given]	Objective signs of PNS involvement (muscle tone, tendon reflexes, muscle wasting, sensory disorders), subjective symptoms; EMG; maximal motor-conduction velocity, abnormal if lower than 5% fiducial limits in normal population; no detail of when tests were performed relative to last exposure or under what conditions	Mixture of solvents in glues; no details of timing of exposure	Age only	"Polyneuropathic " vs normal; prevalence of polyneuropathy higher in exposed (29% vs 17%; $p < 0.05$); polyneuropathy more frequent with age: 38% over age 40, 18% younger ($p < 0.005$); association between age, maximal motor-conduction velocity in exposed and nonexposed; correlation found between duration of exposure, MCV (r = -0.21; no *p* value given)	Unclear how many subjects included; study included n-hexane, solvent not sent to Gulf War and a known cause of peripheral neuropathy
Fagius and Gronqvist, 1978 Sweden	42 plastic-coated sheet production workers at steelworks	42 workers in other sections of steelworks	Clinical examination; questionnaire with information on history, exposure, tobacco, alcohol, symptoms (muscle cramping, pain in arms or legs, pins and needles, numbness, reduced sensation, loss of muscle power, diminished muscle volume); vibration sense; MCV, SCV, laboratory tests	Variety of organic solvents; methyl isobutyl ketone, methyl ethyl ketone; duration of employment 6 months–8 years; individual exposure mapped through estimation of mean daily exposure, each subject given exposure coefficient (product of duration in years and mean exposure in minutes per day)	Exposed, referents matched on age, sex, duration of employment	No overt polyneuropathy; one case of possible polyneuropathy in exposed as defined by symptoms; MCV, two cases of suspected polyneuropathy; two reference subjects had high vibration perception; reference subjects showed longer terminal latency in median nerve when all subjects were assessed and when only those with high exposure in preceding 6 months considered. Vibration perception worse in total group of exposed subjects but not retained when only higher exposure considered; considering only exposure in preceding 6 months, higher vibration threshold of forefinger of exposed than of referents ($p < 0.05$), of styloid process of right radius	Authors conclude "some evidence that exposure to organic solvents has a noxious effect on the peripheral nerve function, but the evidence is weak and no definite conclusions can be drawn"

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Reference	Exposed Population	Nonexposed Population	Health Outcomes or Test Type	Solvent	Adjustment	Results	Limitations
Gregersen et al., 1984 Denmark	65 workers exposed to organic solvents	33 workers not exposed to organic solvents	Testing took place after an exposure free interval of over 40 h and after work; questionnaire for symptoms; neurologic examination; scores developed to quantify impairment	Variety of organic solvents (white spirits, perchloroethylene, styrene, toluene); job information collected in questionnaire; exposure index computed from occupational history, environmental data; other neurotoxic exposure scored	Age, alcohol consumption, brain trauma	No differences between exposure groups– so they were grouped; acute work-related symptoms significantly more common in exposed (no *p* value given); no symptoms or signs of sensory, motor peripheral neuropathy; VPT of exposed group higher than that of nonexposed group but not significant; significant correlation between exposure index, motor symptoms, signs of peripheral neuropathy ($r = 0.21$, $p < 0.1$)	
Mutti et al., 1982 Italy	95 shoe factory workers; exposure duration 1–25 years	52 nonexposed from same factory	MCV; examination by physician	Hydrocarbon mixtures; main source of exposure was evaporation from glued surfaces and open cans containing solvents; environmental concentrations measured for 2 years; overall exposure score calculated	None	Acute symptoms more common among exposed workers; significantly more sleepiness and dizziness; chronic symptoms (weakness, paresthesia, hypoesthesia) more common in exposed; headache, muscle cramps, neurasthenic syndrome, sleep disturbances no different; motor action potentials reduced in median, ulnar nerves; MCV decreased in median, peroneal nerves ($p < 0.05$); MAP duration increased only for ulnar nerve; exposure score, MCV highly correlated ($r = 0.455$; $p < 0.01$	

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Reference	Exposed Population	Nonexposed Population	Health Outcomes or Test Type	Solvent	Adjustment	Results	Limitations
Nasterlack et al., 1999 Germany	401 painters; at least 10 years of work experience	209 construction workers; at least 10 years of work experience	Nerve-conduction velocity; EMG; EEG; symptom questionnaires (Swedish 16-item survey, neurotoxic symptom score, Bf-S[a])	Questionnaire to assess occupational history separately for preceding 12 months and the time before; recent and cumulative solvent exposure score, recorded		Clinical signs of neuropathy in painters: vibration threshold in big toe, lateral ankle, patella; no difference in tendon reflexes or loss of sensitivity; higher frequency of clinically overt polyneuropathy in control subjects than in exposed eight (but not significant); age-adjusted nerve-conduction velocity almost identical in painters and controls; EMG worse in controls than painters; painters had significantly more symptoms than controls; correlation with cumulative exposure index of 0.27 ($p < 0.001$)	

a.Befindlichkeitsskala (Bf-S) is a symptom questionnaire aimed at nonspecific health complaints indicative of somatization.

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Buiatti and colleagues (1978) studied more than 300 Italian shoe and leather workers. The workers were exposed to glues that contained various solvents, including *n*-hexane, ethyl acetate, and traces (below 1%) of benzene, toluol (toluene), and xylol (xylene); all those except *n*-hexane were sent to the Gulf War. Their exposure was measured as amount of glues used per worker per day (in kilograms) and on the basis of air volume per worker and years of exposure to solvents. The outcomes were identified by clinical examination, subjective symptom reporting, and tests of maximal motor-nerve conduction velocity (MCV) (in the extensor digitorum brevis and abductor pollicis brevis muscles). The study did not report the conditions under which the tests were conducted. The investigators examined the relationship between peripheral neuropathy and sex and age but performed no adjustments. They reported a prevalence of peripheral neuropathy of 29% in exposed workers and 17% in the nonexposed group. They also reported that the prevalence increased with increasing exposure but that finding was not evident from the table in the publication. The investigators found that MCV decreased with age, more in workers than in the normal population, and even more in those with peripheral neuropathy. Years of exposure were positively associated with reduced MCV, but this finding was confounded by age. When the subjects were stratified by age, only a slight difference in the slope of the curve of MCV vs years of exposure was observed in those with peripheral neuropathy compared with normal workers. Finally, any findings of peripheral neuropathy in this study might be the result of exposure to *n*-hexane, which is a known cause of peripheral neuropathy.

Fagius and Gronqvist (1978) studied 42 solvent-exposed Swedish steel workers and workers in other parts of the plant. The exposures were primarily to methyl ethyl ketone and trichloroethylene used at the plant for coating the steel with plastic. The duration of employment ranged from 6 months to 8 years. The authors computed exposure in two ways. The first was by calculating an exposure coefficient based on the product of the duration of exposure (in years) and mean exposure per day (in minutes). The other was by calculating daily exposure in the last 6 months. The measures were clinical examination, symptom questionnaire, and nerve-conduction velocity. The clinical examination evaluated muscle power, occurrence of arthropathies, deep tendon reflexes, and senses of touch, temperature, and pain. Loss of function was quantified bilaterally with a score of 0 for normal function, 1 for slight impairment confined to the feet, 2 for more proximal involvement of the legs or involvement of the hands, and 3 for more severe impairment. Unilateral involvement was scored one unit lower. The investigators found a single case of "plausible" peripheral neuropathy and two cases of "suspected' peripheral neuropathy in the 42 exposed workers, although no case definition was presented. None of the reference subjects showed any signs of peripheral neuropathy. Two reference subjects had a high vibration perception threshold (VPT) in the foot, but neither was believed to have sufficient functional impairment to indicate peripheral neuropathy. Overall, the VPT of the group of exposed subjects was significantly different in the forefinger ($p < 0.001$), but the difference disappeared when the groups were analyzed according to increasing exposure.

Gregersen and colleagues (1984) studied 65 workers in Denmark who were exposed to a variety of organic solvents (white spirits, perchloroethylene [tetrachloroethylene], styrene, and toluene). They computed an exposure index that included years of exposure, evaporation, ventilation, frequency of work (percentage of day) with the solvent, skin absorption, frequency of mask use, and danger of the solvent. They were the only investigators who tested study subjects both more than 40 hours after work-related exposure

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and just after work. They performed clinical examination, tested VPT, and administered a questionnaire. During the examination, they computed a sensory score and a motor score of 1 (no signs or symptoms of peripheral neuropathy) to 8 (symptoms and signs involving more than hands and feet for the sensory score or objective paresis of the extremities with muscular atrophy and tendon hyporeflexia or areflexia for the motor score). A combined index was calculated as the average of the sensory and motor scores. The investigators did not find a case of peripheral neuropathy on clinical examination, but they did report a small correlation between the exposure index and a computed combined index for peripheral neuropathy ($r = 0.21$, $p < 0.1$). They found that the VPT of the exposed group was higher than that of the nonexposed group in five of six fields of measurement, but the differences were not statistically significant.

Mutti and co-workers (1982) studied 95 shoe-factory workers who were exposed to various solvents and 52 nonexposed workers in the same factory. Their duration of exposure ranged from 1 to 25 years. The exposed workers were exposed to hydrocarbon mixtures consisting of *n*-hexane, cyclohexane, methyl ethyl ketone, and ethyl acetate; most of the constituents are known to cause peripheral neuropathy. Factory environmental conditions had been measured regularly over the 2 years before the study. An exposure score was computed as the product of number of years in the job and median hygienic effect (the ratio of the measured concentration of the compound and its threshold limit value). The study included clinical examination, a symptom questionnaire, and tests of nerve-conduction velocity. Symptoms present during work hours—sleepiness, dizziness, and headache—were classified as acute; and weakness, paresthesia, hypoesthesia, muscular cramps, neurasthenic syndrome, and sleep disturbances were classified as chronic. Nerve-conduction velocities were tested with workers in an air-conditioned temperature-controlled room at 24°C. On clinical examination, the investigators did not report any cases of peripheral neuropathy among the exposed workers, although they found a higher prevalence of self-reported acute symptoms during work (sleepiness and dizziness) and chronic symptoms—such as weakness in limbs, paresthesia and hypoesthesia—but not cramps, neurasthenic syndrome, or sleep disturbances. The median nerve-conduction velocity was decreased in the exposed subjects (54 mm/s vs 57 mm/s, $p < 0.01$), as was the amplitude (7.69 mV vs 10.83 mV, $p < 0.01$). For the ulnar nerve, both the amplitude (6.17 mV vs 8.08 mV, $p < 0.01$; and duration (13.89 ms vs 12.63 ms, $p < 0.01$) were significantly decreased. An association was also found between exposure score and median nerve-conduction velocity ($r = 0.455$, $p < 0.01$); surprisingly, no association was found between MCV and age. Adjustment for confounding variables was not mentioned.

Nasterlack and co-workers (1999) studied 401 painters with 10 years or more of work experience in Germany. The painters were compared with 209 construction workers. Indexes of exposure were computed for recent exposure (within the last 12 months) and exposure before that time. Painters were classified as being highly exposed if their exposure coefficient was at or above the upper 20th percentile. A clinical evaluation was performed with additional tools: two symptom questionnaires (the Swedish 16-item survey for chronic neurotoxicity and the neurotoxic-symptoms score), neurobehavioral tests, nerve-conduction velocity measurement, EEG, and EMG. This is the only solvent study that used EMG; the results of EMG were classified as normal, borderline, or pathologic. The publication states that subjects were tested "under temperature controlled conditions," but no further details of the test conditions were reported. The authors found a higher, but nonsignificant, frequency

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of overt peripheral neuropathy in the nonexposed subjects than in the painters (2.7% vs 1.7%). However, the subjective symptoms from the 16-item symptom questionnaire were significantly more frequent in the painters than in the nonexposed subjects. There was also a small but statistically significant correlation between symptoms reported on the 16-item survey and the coefficient of exposure ($r = 0.27$, $p < 0.001$). Almost identical age-adjusted nerve-conduction velocities were found. However, the prevalence of low velocity (bottom 20th percentile) in at least two nerves was significantly more common among the painters. The authors found that 86% of painters and 62% of construction workers classified as having normal electromyograms; the statistical significance of this result was not reported.

Summary and Conclusion

None of the five studies described above was appropriately designed to determine whether peripheral neuropathy is a long-term effect of exposure to solvents sent to the Gulf War. The studies were beset by a small range of outcome measures or by insufficient documentation of exposure or design. Furthermore, the findings from the five studies are inconsistent. No particular outcome was repeatedly associated with exposure to solvents. In three of the studies, the authors themselves commented on the paucity of findings. Gregersen and co-workers (1984) reported that the observed neurotoxic signs were only mildly correlated with exposure levels in the exposed group. Nasterlack and co-workers (1999) reported no overall effects of exposure on nerve-conduction velocities, and they were unable to come to a conclusion on either the time course or reversibility of the signs and symptoms. Only Fagius and Gronqvist (1978) found a weak association between exposure to solvents and some abnormal findings.

In contrast, two studies of shoe and leather workers reported more significant findings, including statistically significant slowing of nerve conduction (Buiatti et al., 1978; Mutti et al., 1982). Indeed, Buiatti and co-workers found that more than one-fourth of workers had peripheral neuropathy, but the study had design limitations. Neither study made adjustments for known confounders.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and peripheral neuropathy.

NEUROBEHAVIORAL EFFECTS

Neurobehavioral (NB) effects are broadly defined to include changes in cognition, mood, and behavior that are mediated by the central nervous system. NB effects are measured via symptom questionnaires or validated tests. NB tests and the functional domains they measure are described in Appendix F. NB effects of exposure to sarin, an OP nerve agent, were evaluated in an earlier IOM committee report (IOM, 2000). This section evaluates the accumulated evidence from studies of Gulf War veterans and workers exposed to OP insecticides and solvents.

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Studies of Gulf War Veterans and Neurobehavioral Effects

The body of Gulf War studies that examined NB effects of insecticide or solvent exposures is for the most part cross-sectional with respect to exposures and outcomes and frequently based on self-reports. Because of the unexplained nature of veterans' symptoms, many of which are neurobehavioral, investigators strove to define new syndromes or to establish variants of existing syndromes (Appendix A). The methods of measuring and analyzing NB effects in veterans varied greatly, sometimes including a battery of validated NB tests and more frequently including a host of symptom checklists. Investigators grouped or clustered symptoms into particular NB functional domains in different ways (for example, by factor analysis or a priori symptom grouping). Furthermore, insecticides and solvents typically constituted only a small subset of the potential agents to which Gulf War veterans may have been exposed. The exposure classification was general, such as "pesticides," and the level of exposure was rarely assessed.

This subsection describes several studies, beginning with the few that used NB tests, before proceeding to studies of symptom groupings covering what has been termed chronic multisymptom illness, symptoms of impaired memory and concentration, and finally symptoms of dizziness and impaired balance. The committee selected those general categories for ease of comparison with the occupational studies of insecticides and solvents. We concentrate here on Gulf War studies that examined exposure–symptom relationships, and we evaluate findings only for relevant pesticides or solvents. The studies covered here are presented in Table 7.4 and are categorized according to whether they were population-based or military-unit-based.

Studies with NB Testing

Two studies of veterans used NB testing to address possible effects of insecticide exposure during the Gulf War. The study with the stronger methods found an association between pesticide exposure and abnormal scores on the subscales of the Profile of Mood States (POMS) but found no associations with abnormalities on other components of a comprehensive NB test battery (White et al., 2001). The other study showed no associations between pesticide exposure and handgrip strength (Kaiser, 2000). Neither study specifically asked about veterans' exposures to relevant solvents. Two followup studies by Haley and colleagues included NB testing but did not evaluate associations between pesticide or solvent exposure and test abnormalities (Haley et al., 1997b; Hom et al., 1997).

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TABLE 7.4 Gulf War Studies and Neurobehavioral Effects

Reference	Population	Self-Reported Exposure to Relevant Pesticides or Solvents	Health Outcome or Test Type	Results	Limitations
Population-Based Studies					
Unwin et al., 1999 UK	2735 UK veterans deployed to Gulf War vs 2393 deployed to Bosnia vs 2422 deployed elsewhere	Four of 29 related to pesticides or solvents: “personal pesticides,” "other paints or solvents," "handled prisoners of war," "pesticides on clothing or bedding"	Symptom questionnaires, exposure questionnaire	All solvent or pesticide exposures associated with chronic multisymptom syndrome, posttraumatic stress reaction;physical functioning in all three cohorts	Self-reported symptoms and exposures; lack of adjustment for interrelationships between multiple exposures; use of p value of 0.05 despite multiple comparisons
Cherry et al, 2001a UK (see also Table 7.1)	4795 UK veterans deployed to Gulf War (and validation cohort of 4750) vs 4793 UK veterans not deployed to Gulf War	Four of 14 related to pesticides or solvents: “days exposed to handling pesticides,” “days living in quarters sprayed with insecticides,” “days respraying vehicles,” “days applying insecticide to skin”	Symptom questionnaire, exposure questionnaire; surveys completed 7 years or more after war	“Concentration” factor not associated with any relevant pesticide or solvent exposure in multivariate regression analysis; “neurologic” factor associated with pesticide handling in multivariate regression analysis ($p <$ 0.001), but no clear dose–response relation; “neurologic” factor not associated with other pesticide, solvent exposures in multivariate analysis	Self-reported symptoms and exposures
Iowa Persian Gulf Study Group, 1997 US	1896 deployed veterans from Iowa as home of record vs 1799 nondeployed veterans from Iowa as home of record	Two of over 20 items related to solvents or pesticides: “solvents/petrochemicals,” “pesticides”	Symptom questionnaires, exposure questionnaire	Symptoms of cognitive dysfunction associated with higher prevalence of exposure to “solvents/petrochemicals” (prevalence difference of 6.6%, $p < 0.001$), “pesticides” (prevalence difference of 14.2%, $p < 0.001$)	Self-reported symptoms and exposures; low proportion of minority-group subjects; internal validation of responses not assessed; no adjustment for multiple comparisons; multiple associations between variety of exposures and variety of outcomes

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Reference	Population	Self-Reported Exposure to Relevant Pesticides or Solvents	Health Outcome or Test Type	Results	Limitations
Goss Gilroy Inc., 1998 Canada	3113 Canadian veterans deployed to Gulf War vs 3439 deployed elsewhere	Over 30 exposures divided into six categories; one category labeled "CNS factors" includes five relevant solvent or pesticide exposures (of eight total): "other paints and solvents," "food contaminated with . . . other chemicals," "personal pesticides," "flea collars," "pesticides on bedding or clothing"	Symptom questionnaires, exposure questionnaire	Exposure to "CNS factors" associated with cognitive dysfunction (OR = 1.45, 95% CI = 1.19–1.76)	Self-reported symptoms and exposures; subset of Canadian veterans not exposed to many agents (because they were based at sea) reported symptoms as frequently as did land-based veterans; no adjustment for multiple comparisons; multiple associations between various exposures and various outcomes; not clear which pesticide or solvent exposures were related to outcome
Kang et al., 2002	11441 US veterans deployed to Gulf War vs 9476 Non-Gulf deployed Nested case–control	Five of 23 exposures related to solvents: "personal pesticides, including creams, sprays and flea collars," "contact with prisoners of war," "food contaminated with smoke, oil, or other chemicals," "other paint or solvent or petrochemicals substances," "chemical agent resistant compound paint."	Factor analysis, symptom questionnaires; exposure questionnaire	Exposure to CARC paint and one other solvent-related exposure at least 3 times more common in 277 Gulf-War deployed veterans than in controls who met case definition with all these symptoms: loss of balance or dizziness, speech difficulty, sudden loss of strength, tremors or shaking	Self-reported symptoms and exposures; no analysis for dose-response
Military-Unit-Based Studies					
White et al., 2001 US (same cohort as Proctor et al., 1998)	273 US deployed veterans from Massachusetts (Fort Devens) and New Orleans vs 50 Germany-deployed veterans	One of eight environmental exposures related to pesticides or solvents: "pesticides"	15 NB tests: WAIS-R, tests of attention, executive function, motor-psychomotor, visuospatial, memory, mood (POMS), motivation; exposure questionnaires; diagnostic interviews for PTSD	Exposure to "pesticides" associated with significant differences on all five POMS subscales	Self-reported exposures; limited representativeness of entire Gulf War cohort
Kaiser, 2000 US (same cohort as Gray et al., 1999)	527 active-duty Seabees formerly deployed to Gulf War vs 969 nondeployed veterans from same Seabee commands	Two exposures related to pesticides or solvents: "insecticide spray," "burning insecticide coils"	Handgrip strength	Handgrip strength not associated with exposure to insecticide spray, burning of insecticide coils, or use of pyridostigmine bromide	Moderate to low response rate; exclusion of veterans no longer in active service; self-reported exposures; limited representativeness of entire Gulf War cohort
Nisenbaum et al., 2000 US	1002 veterans from four Air Force units; nested case–control survey of 459 Gulf	One of six environmental exposures related to pesticides or solvents:	Symptom questionnaires, exposure questionnaire	Severe and mild-moderate cases of chronic multisymptom illness	Self-reported symptoms and exposures; no reporting on exact time of exposure; exclusion of Gulf War veterans no longer in

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Reference	Population	Self-Reported Exposure to Relevant Pesticides or Solvents	Health Outcome or Test Type	Results	Limitations
(followup to Fukuda et al., 1998)	War veteran cases of chronic multisymptom illness vs 543 controls without chronic multisymptom illness	"regular use of insect repellent"		associated with "regular use of insect repellent" (OR = 2.4, 95% CI 1.3–4.5)	active service; no adjustment of *p* value despite multiple comparisons; limited representativeness of entire Gulf War cohort
Haley and Kurt, 1997 US	23 veterans with up to three newly defined syndromes (derived from factor analysis) vs 229 veterans without newly defined syndromes	Five of 18 related to pesticides or solvents: "DEET-containing insect repellent," "environmental pesticides," "pesticides in uniforms," "pesticides in flea collars," "CARC paint on vehicles"	Symptom questionnaire, exposure questionnaire	Among 20 veterans with this syndrome, wearing flea collars more common (RR = 8.7, 95% CI = 3.0–24.7)	Self-reported symptoms and exposures; no control group in original cohort; limited representativeness of entire Gulf War cohort
Gray et al., 1999 US	527 active-duty Seabees formerly deployed to Gulf War vs 969 nondeployed veterans from same Seabee commands	Four of 30 exposures related to pesticides or solvents: "insecticide spray," "direct contact with prisoners of war," "burning insecticide," "wore a flea collar for more than one day"	Symptom questionnaire, exposure questionnaire; clinical examination; handgrip strength; pulmonary function; serum collection	"Contact with POWs;" only pesticide or solvent exposure common enough to be analyzed with 10 other exposures for exposure–symptom relationships; "Contact with POWs" significantly associated with forgetfulness (RR = 2.8) and confusion (RR = 5.0)	Self-reported symptoms and exposures; Potential recall bias in symptom reporting; moderate to low response rate; exclusion of veterans no longer in active service; exclusion of several potentially important exposures from analysis; limited representativeness of entire Gulf War cohort
Proctor et al., 1998 US	300 US deployed veterans from Massachusetts (Fort Devens) and New Orleans vs 48 Germany-deployed veterans	One of eight environmental exposures related to pesticides or solvents: "pesticides"	Symptom questionnaires, exposure questionnaires; clinical evaluations used for end points other than peripheral neuropathy	Exposure to "pesticides" associated with neurologic symptom group (headaches, numbness in arms or legs, dizziness) ($p = 0.007$), musculoskeletal symptom group ($p = 0.001$); "pesticide" exposure not significantly related to neuropsychologic group (such as difficulty in concentrating, confusion) or psychologic symptoms (such as inability to fall asleep, anxiety, depression)	Self-reported symptoms and exposures; moderate to low response rate; limited representativeness of entire Gulf War cohort

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White and colleagues (2001) reported NB findings from a larger study of the Ft. Devens and New Orleans cohorts described earlier (Proctor et al., 1998). Exposure during the Gulf War was assessed with a questionnaire that addressed eight different agents, one of which was to "pesticides." Veterans completed a 2-hour NB test battery designed to assess all major functional domains of general intelligence, attention and executive function, motor ability, visuospatial processing, verbal and visual memory, mood, and motivation (Appendix F). Specific tests included subsets of the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale, the POMS, the Purdue pegboard test, and tests of attention and reaction time (digit-span, trail-making, and continuous-performance tests), serial arithmetic, card-sorting, finger-tapping, and block design. All results were corrected for the presence of posttraumatic stress disorder, or PTSD (via the Clinician Administered PTSD Scale) and depression (via the Structured Clinician Interview for DSM-IV) because both have been shown to influence NB test performance in veterans. The study found that self-reported exposure to pesticides was associated with abnormal scores on all the POMS subscales but was not associated with abnormalities in any of the other NB tests.

Kaiser (2000) examined the association between self-reported exposure and results of a battery of questionnaires, clinical measurements, and handgrip strength. The study examined a sample of active-duty Seabees still serving in 1994. Gulf War veterans with more severe symptoms were likely to have been excluded because they were no longer on active-duty status. Handgrip strength was not associated with exposure to insecticide spraying, burning of insecticide coils, or use of pyridostigmine bromide (PB), which was used as prophylaxis for nerve-agent exposure. The actual focus of the study was PB, a carbamate.[6] Multivariate models showed no interaction between PB and insecticide spraying or burning of insecticide coils.

Haley and colleagues published several articles comparing a subset of the veterans they identified as having one of their three syndromes with unaffected veterans from the same battalion. The three syndromes they had previously identified were categorized as "impaired cognition," "confusion–ataxia," and "arthro-myo-neuropathy" (Haley et al., 1997a). The general methods of identifying the syndromes are discussed earlier in this chapter and in Appendix A.

Two publications by Haley and colleagues (1997a,b) included NB testing. Both compared 23 veterans with the highest scores on the first three of their syndromes with 10 unaffected controls—matched by age, sex, and educational level—who were selected from 70 veterans who had been deployed to the Gulf War and had reported no serious health problems in the prior study. An additional 10 unaffected, matched controls were selected from veterans who had not been deployed to the Gulf War. Veterans with one of the three syndromes had more abnormal scores on global measures of brain dysfunction, tests of audiovestibular function, and somatosensory, visual, and brainstem auditory evoked potentials (Haley et al., 1997a,b). In a separate paper on what appears to be the same set of veterans, Hom and colleagues (1997) found "a generalized pattern of neuropsychological deficit" among the veterans with one of the three syndromes, as measured by a number of tests, including the Halstead Impairment Index and three subscales of the WAIS. Neither of the articles reported on pesticide or solvent exposures of the affected veterans. Thus, although Haley's previous report had shown associations between the three syndromes and some pesticide exposure during the Gulf War (Haley and Kurt, 1997), the analysis in these

[6]PB was studied by the previous IOM Gulf War and Health committee (IOM, 2000).

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two other studies did not address associations between NB test abnormalities and Gulf War exposures.

Summary and Conclusion

In summary, only one of the studies that performed NB tests was sufficiently large and well designed to examine NB test performance in relation to pesticide or solvent exposure in the Gulf War (White et al., 2001). Although the study contained an array of NB test measures, it examined only one relevant exposure—namely, to "pesticides." That study found that self-reported exposure to pesticides was associated with mood symptoms as assessed by the POMS but not with any other NB tests. Nevertheless, it lacked specificity about the nature or degree of pesticide exposure, and the sample was military-unit-based, rather than population-based, so the findings are not necessarily representative of the entire Gulf War cohort. The other studies had more serious design limitations—for example, there were too few outcome measures, or the relationship between outcome and exposure of interest was not measured. The committee was not able to draw particular conclusions from these studies.

"Chronic Multisymptom Illness"

One of the first studies that endeavored to classify Gulf War veterans' symptoms into a new syndrome created a case definition for "chronic multisymptom illness." The case definition, which was based on factor analysis and other methods, required at least two of these three categories of symptoms to have been present for at least 6 months: fatigue, mood–cognition symptoms (such as feeling depressed and having difficulty in remembering or concentrating), and musculoskeletal symptoms (joint pain, joint stiffness, or muscle pain) (Fukuda et al., 1998). Conducted by the Centers for Disease Control and Prevention (CDC), the study focused on active-duty Air Force National Guard and three other Air Force units, two of which (from Florida) had not been deployed to the Persian Gulf. Because a sizable percentage of the nondeployed veterans also met the case definition, the study concluded that the case definition could not uniquely characterize veterans' unexplained illnesses (Appendix A). Nevertheless, the case definition has been used since then because multisymptom illnesses are more prevalent among Gulf War veterans than among nondeployed veterans.

Two studies of Gulf War veterans searched for associations between chronic multisymptom illness and pesticide or solvent exposure (Nisenbaum et al., 2000; Unwin et al., 1999). Nisenbaum and colleagues (2000) performed a nested case–control study using the same cohort studied by Fukuda and colleagues (1998). They examined the association between chronic multisymptom illness and six environmental exposures, only one of which was relevant to the committee ("used insect repellent on a regular basis"). The sample, as noted above, was drawn from a military population still active in 1994. Cases of chronic multisymptom illness were classified as severe if each case-defining symptom was rated by veterans as severe; if not, the case was rated as mild–moderate. The study compared 459 Gulf War veterans with chronic multisymptom illness and 543 without the illness. In univariate analyses, all exposures were associated with mild–moderate or severe cases. In multivariate analysis that adjusted for all other exposures—and for age, sex, smoking, rank, and military unit—the association with regular use of insect repellent (and two other

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environmental exposures) remained significant ($p < 0.05$). The adjusted ORs were 2.4 (95% CI = 1.3–4.5) for severe cases and 1.7 (95% CI = 1.2–2.3) for mild–moderate cases of multisymptom illness. The interaction of insect repellent and pyridostigmine bromide was found not to be significant.

Unwin and colleagues (1999) studied three randomly selected samples of UK military personnel deployed to the Gulf War. The first was chosen from male and female veterans deployed from September 1, 1990 to June 30, 1991. They were compared with two comparison cohorts serving elsewhere during the same period: one in Bosnia and one in the armed forces but not deployed to the Gulf War. All three samples received a questionnaire by mail. The questionnaire included 29 items concerning possible agents to which Gulf War veterans may have been exposed; four of the agents were related to insecticides and solvents (Table 7.4). Analyses were restricted to responses from men, and the level of significance was set at 0.05 although multiple comparisons were performed. All four relevant agents were associated with chronic multisymptom illness regardless of deployment status. The ORs comparing exposed and nonexposed for each cohort of Gulf War-deployed and non-Gulf War-deployed veterans were weak to moderate (1.7–2.2).

Summary and Conclusion

In summary, two studies of Gulf War veterans using the same empirically derived case definition for chronic multisymptom illness found some associations with pesticide exposure. The possibility of a type I (false-positive) error exists for both studies, in that both made multiple comparisons without adjustment for the number of comparisons. Also, recall bias is a possibility inasmuch as both studies used self-reports of exposure. One study (Unwin et al., 1999) used rigorous methods and a random sample of UK Gulf War veterans; it found an association between chronic multisymptom illness and each of the relevant pesticide or solvent exposures, but a similar association was found with all but one of the other exposures. Therefore, the association found in this study might have been due to confounding by some other exposure that was correlated with the pesticide and solvent exposures. The second study (Nisenbaum et al., 2000) used a less representative sample that was likely to have excluded people with the highest levels of disability, and it used the same sample whose clinical findings were initially used to define cases of chronic multisymptom illness. An association between chronic multisymptom illness and pesticide exposure persisted after adjustment for the presence of other exposures. Still, no definitive conclusions can be drawn from these studies.

Symptoms Related to Memory and Concentration

Six studies of Gulf War veterans that used widely varied methods were reviewed by the committee for relationships between pesticides or solvents and symptoms related to memory and concentration. Two of the studies used factor analysis to group symptoms, the others clustered symptoms by using a priori categories.

Cherry and colleagues (2001a) studied illnesses and exposures in a population-based study of all UK veterans deployed to the Persian Gulf. (Study details were described in the discussion of peripheral neuropathy earlier in this chapter.) The study derived symptom groups by a factor analysis of symptoms from two random samples of all UK veterans stratified by age, sex, and rank. One of the seven factors derived from factor analysis and

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labeled as "concentration" clustered 10 symptoms: difficulty in concentrating, poor memory, needing to make notes to remember things, needing to check on things already done, clumsiness, slurring words, other people noting a poor memory, difficulty in grasping meanings, difficulty in making decisions, and difficulty in saying what was intended (Cherry et al., 2001b). The "concentration" factor was not found to have an association with any pesticide or solvent exposure in the multivariate regression analysis.

Haley and Kurt (1997) linked one of their factor-analysis-derived syndromes to wearing of flea collars that contained insect repellent. Of the six new syndromes identified by factor analysis, syndrome 1 ("impaired cognition") consisted of nine symptoms: distractibility, short-term and long-term memory problems, depression, fatigue, slurring of speech, confusion, insomnia, and headache (Haley et al., 1997a). Syndrome 1 was about 9 times more common among those who reported wearing flea collars than among those who never wore them (RR = 8.7, 95% CI = 3.0–24.7). A dose-response trend was also found in the syndrome 1 case group: 3% (seven of 229) of those who reported never wearing flea collars were found to have the syndrome, compared with 18% (three of 17) of those who wore them but not next to their skin, and 67% (two of three) who reported sometimes wearing flea collars next to their skin. No association was found between syndrome 1 and the three other pesticide exposures or the one solvent exposure relevant to the committee.

Gray and colleagues (1999) examined symptoms and exposures in active-duty Seabees who were still serving in 1994; Gulf War veterans with more severe symptoms were likely to have been excluded. The exposure questionnaire asked about 30 different exposures, but the authors chose to limit further analyses to the subset of 11 exposures that had an OR greater than 3 (Gulf War-deployed vs nondeployed veterans) and that were reported by more than 5% of Gulf War veterans. Because of those restrictions, associations between symptoms and three relevant pesticide exposures were not examined. The only pesticide-related exposure analyzed was "direct contact with prisoners of war" (POWs). The handling of POWs included delousing with pesticides, so veterans exposed to POWs may have had some pesticide exposure. Direct contact with POWs was significantly associated with only four symptoms in the univariate analysis. Two of the four were forgetfulness (RR = 2.8) and confusion (RR = 5.0), both of which were reported as having confidence intervals that excluded 1.[7] (The other two symptoms were roving joint pain and sore throat.) The same investigators also performed a factor analysis of symptoms that was published separately (Knoke et al., 2000). They noted that one of the five factors they identified bore a close resemblance to syndrome 1 (as identified by Haley and Kurt, described earlier), but they did not examine relationships between symptom factors and exposures.

Proctor and colleagues (1998) studied veterans from Massachusetts and New Orleans in a study described earlier. In their multiple-regression analysis, which controlled for associations between self-reported exposures and for other factors (listed above) and set p at 0.05, the "neuropsychologic" group of symptoms was not significantly associated with exposure to "pesticides." The "neuropsychologic" group was composed of three symptoms: difficulty in learning new material, difficulty in concentrating, and confusion.

The "Iowa study" (1997) was a large population-based study of US Gulf War veterans. It surveyed a representative sample of 4886 military personnel who had active service during the Gulf War and who listed Iowa as their home of record at the time of enlistment (Iowa Persian Gulf Study Group, 1997). The study examined the health of military

[7]Actual confidence intervals not reported, except that they excluded one.

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personnel from all branches of service who were still serving or had left service. The sample was randomly selected from and therefore representative of about 29,000 military personnel and was stratified by age, sex, race, rank, and range of military service. Among other findings (see Appendix A), the two groups of Gulf War veterans reported roughly twice the prevalence of symptoms suggestive of cognitive dysfunction compared with nondeployed veterans.[8] That was the largest prevalence difference among all study findings. Researchers had grouped sets of symptoms from their telephone-administered symptom checklists into a priori categories of diseases or disorders. The Iowa study assessed exposure–symptom relationships by asking veterans to report on more than 20 agents, two of which were relevant to the committee: "solvents/petrochemicals" and "pesticides." Researchers found that deployed veterans with symptoms of cognitive dysfunction had a higher prevalence of reporting solvent or petrochemical exposure than nondeployed veterans (exposure-prevalence difference, 6.6%; $p < 0.001$). They also found them to have a higher prevalence of reporting exposure to pesticides (difference, 14.2%; $p < 0.001$).

A study of all Canadian Gulf War veterans (1994) compared them with a large sample of Canadian forces serving elsewhere at the time of the Gulf War (Goss Gilroy Inc., 1998). Respondents filled out a long questionnaire. The authors defined the outcome of "cognitive dysfunction" as requiring at least one of the following symptoms or combinations of symptoms and severity: amnesia or severe memory loss (no severity scale); confusion or disorientation ("moderately" or more); any two of eight cognitive symptoms with a severity of "moderately" or more, or one of the eight with a severity of "quite a bit" or "extremely." A severity greater than "moderately" for confusion and disorientation occurring alone qualified a person as cognitively impaired, as did the presence of amnesia or severe memory loss alone. The authors did not report on associations with single pesticide or solvent exposures but grouped a number of pesticide and solvent exposures as "CNS factors." They reported an association between "CNS factors" and cognitive dysfunction, with an OR of 1.45 (95% CI = 1.19–1.76).

Summary and Conclusion

In summary, difficulties with memory and concentration have been consistently shown to be more prevalent among Gulf War veterans than among comparison groups. However, the evidence of an association with pesticide or solvent exposure is inconsistent. For example, the strongest study, a population-based study of UK veterans (Cherry et al., 2001a), failed to show an association. Another study (Haley and Kurt, 1997) found an association only with the use of flea collars but failed to demonstrate an association with three other pesticide exposures or with a solvent exposure. A study by Proctor and colleagues (1998) using a multivariate analysis correcting for exposure to other agents also failed to demonstrate an association. Two population-based studies (Goss Gilroy Inc., 1998; Iowa Persian Gulf Study Group, 1997) showed an association between memory or concentration symptoms and pesticide exposure, broadly defined; both used univariate analyses but did not take into account the number of comparisons made between various

[8]Precise symptoms constituting cognitive dysfunction were not reported. After a veteran identified himself or herself as having the requisite set of symptoms, researchers analyzing responses considered the veteran to have symptoms "suggestive" of or consistent with a particular disorder but not to have a formal diagnosis of the disorder.

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exposures and various outcomes, which may have produced type I errors (false-positive results). No definitive conclusions can be drawn from these studies.

Symptoms Related to Dizziness and Balance

Cherry and colleagues (2001a,b) found that one of their factors identified by factor analysis, which included dizziness and balance, was associated with pesticide exposure. They studied illnesses and exposure in a population-based sample of all UK veterans deployed to the Persian Gulf. (Study details were described earlier.) One of the seven factors, "neurologic," clustered 13 symptoms, including problems in buttoning, difficulty in rising from a chair, fainting, feeling too weak to complete tasks, losing balance, difficulty in bringing objects down from above the head, double vision, shortness of breath when walking, unsteadiness when walking, and feeling dizzy (Cherry et al., 2001b). Pesticide handling was significantly related to the neurologic factor in the multivariate regression analysis. No clear dose–response association was found with days of exposure to pesticide handling. Personal use of insect repellent and other pesticide and solvent exposures were not statistically significant associated with the neurologic factor.

Kang and colleagues (2002), in a population-based study of US veterans, found that one of their factors identified by factor analysis, which included dizziness and balance, was associated with solvent exposure. The study was the largest and most representative of US veterans (11,441 deployed and 9476 nondeployed veterans). The factor analysis of 47 symptoms identified six factors, only one of which contained a cluster of symptoms that did not load on any factors in the nondeployed Gulf War veterans. The symptoms in the cluster were: loss of balance–dizziness, speech difficulty, blurred vision, and tremors–shaking. A group of 277 deployed veterans (2.4%) and 43 nondeployed veterans (0.45%) met a case definition subsuming all four symptoms. A nested case–control analysis was performed to determine which of 23 self-reported exposures were more common among Gulf War veterans who met the case definition than among Gulf War veterans who lacked any of the symptoms. Of the nine exposures that were at least three times higher among cases, two were solvent-related: CARC paint (51.2% in cases vs 16.3% in controls) and food contaminated with oil smoke (73.4% in cases vs 20.6% in controls). No pesticide-related exposures were reported three or more times more frequently in cases versus controls. A dose-response relationship was not studied, because of the nature of the dataset regarding self-reported exposure. NB testing was not performed, but is likely to be in the final phase of this study.

Two other less representative US studies using factor analysis did not identify a factor related to dizziness and balance. The CDC study (Fukuda et al., 1998), which attempted to define a chronic multisymptom illness, included only a single question that addressed "dizziness or trouble maintaining balance." No corresponding dizziness or balance-related factor was extracted in the factor analysis by Knoke and colleagues (2000). Haley's "syndrome 1" (Haley et al., 1997a) contains one symptom (slurred speech) that could overlap with dizziness and balance problems, but the syndrome consists mainly of attention, reasoning, and memory problems that were grouped in a separate "concentration" cluster in the Cherry study (2001b, see above). Haley's "syndrome 2" ("confusion–ataxia") also has several symptoms of balance and coordination problems, but none of the pesticide or solvent exposures was related to this particular syndrome. A separate publication by Haley and colleagues (Roland et al., 2000), using audiovestibular testing, reported on the

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vestibular complaints of 23 veterans with syndromes 1–3 compared with 20 unaffected controls; the study did not relate vestibular dysfunction to exposures.

In addition to the study by Cherry and colleagues, one study (Proctor et al., 1998) examined associations between pesticide exposure and individual symptoms of dizziness and balance problems. The neurologic group of symptoms included headache, numbness in arms or legs, and dizziness or lightheadedness and thus bore some similarity to Cherry and colleagues' neurologic factor and peripheral factor. Exposure to "pesticides" in the Proctor et al. study was associated with their neurologic symptom group ($p = 0.007$).

Summary and Conclusion

In summary, two population-based studies did identify a dizziness or balance factor among deployed veterans. In the study by Cherry and colleagues (2001a), some pesticide exposures were associated with the symptom factor related to dizziness and balance; the study did not find a dose–response relationship, and found no relationship to solvent exposure. In the study by Kang and colleagues (2002), a small subset of veterans who met a case definition including dizziness and balance problems were far more likely to report solvent exposures. The symptom–exposure findings from those two studies were considered by the committee in its evaluation of the entire body of studies on NB effects of pesticide and solvent exposure (see next sections). Dizziness and balance symptoms were not found in two other, yet less representative, factor-analysis studies of Gulf War veterans (Fukuda et al., 1998; Knoke et al., 2000), but these studies excluded veterans who had left the service. Because dizziness and balance symptoms are potentially quite disabling, a study using only Gulf War veterans who remained in active service could have missed the presence of this factor. One study reported some dizziness and balance symptoms in one of its factor-analysis syndromes, but the syndrome was not associated with pesticide or solvent exposure. No definitive conclusions can be drawn from these studies, but two of the studies (Cherry et al., 2001a; Kang et al., 2002) are incorporated into the committee's conclusions in the next sections of this chapter.

OP INSECTICIDES AND NEUROBEHAVIORAL EFFECTS

This section contains the committee's evaluation of two major types of studies on OP insecticides and neurobehavioral effects: studies of workers with past OP poisoning who had been hospitalized and treated for the acute cholinergic syndrome and studies of workers with chronic exposure to OP insecticides but no documented episode of past OP poisoning.

Limitations of Studies of Insecticides and Neurobehavioral Effects

The studies evaluated here are mostly cross-sectional studies. Various limitations apply to cross-sectional studies in general and to the particular types of studies of OP-poisoned workers or workers with chronic exposure without past poisoning.

A general limitation of occupational cross-sectional studies is that the study population frequently includes workers that are "healthier" and therefore are able to continue working (the "healthy-worker effect," see Chapter 2). Workers who become ill leave the workforce and are not usually included in a cross-sectional study population.

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Another potential limitation is related to bias in the selection of the groups. Different demographic characteristics of the control group (such as education and language) and the exposed group can lead to differences in performance on NB testing.

In several of the studies of past OP poisoning, a group is identified through registries of workers with a history of having been poisoned (e.g., Savage et al., 1988; Steenland et al., 1994). One potential limitation of this type of study is selection bias. Frequently, only about half of poisoned workers are locatable and available to participate. That raises the possibility that those with the most symptoms are more eager to participate. In addition, many of the poisoned subjects have had years of chronic exposure, and that makes it difficult to distinguish whether adverse effects are attributable to the poisoning or to years of chronic, lower-level exposure. Although details of the specific exposure are not always available, exposure misclassification of workers poisoned with OP insecticides or carbamates is unlikely because they were medically evaluated and treated for acute cholinergic signs and symptoms while spraying insecticides.

The committee's charge to examine *long-term* effects created another type of limitation. Most studies in the occupational literature are of workers with both past and current insecticide exposure. The observed NB findings may be long-term effects of past exposure or short-term effects of current exposure (which might resolve once exposure ceases). The only way to separate out long-term from short-term effects is to examine workers with only past exposure. Therefore, the committee selected for its evaluation only studies of workers after an exposure-free interval (e.g., Rosenstock et al., 1991) or studies that used workers' AChE concentrations to exclude those with current (or recent) exposure. For example, Savage and colleagues (1988) studied long-term effects by confirming that AChE in exposed and referent subjects did not indicate recent exposure.

OP Exposure and Neurobehavioral Effects With a History of Past OP Poisoning

Four studies examined populations of workers (mostly Hispanic males) previously treated for acute OP-insecticide poisoning (Reidy et al., 1992; Rosenstock et al., 1991; Savage et al., 1988; Steenland et al., 1994). OP poisoning results in symptoms or signs of the acute cholinergic syndrome (Chapter 3), which, because of its life-threatening nature, typically requires hospitalization. Two of the four studies documented AChE concentrations to confirm past poisoning or the absence of recent exposure (Savage et al., 1988; Steenland et al., 1994). In addition to acute poisoning, most of the workers in these studies had years of chronic exposure. Evaluations were conducted within 2 years of the last poisoning in one study (Reidy et al., 1992) and 1–11 years after poisoning in the other studies. Comparison subjects (not OP-poisoned) were selected from friends of the poisoned group in three of the four studies. Comparison subjects frequently also had a history of insecticide exposures or agricultural jobs even if they had no history of treatment for OP poisoning. For assessment of outcome measures, all the studies used standardized NB test batteries (sometimes in Spanish) covering an array of NB domains (language, attention and executive functioning, memory, visuomotor and visuospatial ability, and motor skills). Various questionnaires on CNS symptoms, including mood, were also incorporated into the design and analysis. Overall, OP-poisoned subjects performed worse on NB tests and reported more symptoms than comparison subjects. The studies, their strengths, and their limitations are described below in Table 7.5.

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TABLE 7.5 Neurobehavioral Effects with History of Past OP Poisoning

Reference	Population: Exposed	Population: Control	Health Outcomes or Test Type	OP Insecticide Exposure	Adjustment	Results	Limitations
Savage et al., 1988	100 male workers from Colorado and Texas registry of OP-insecticide poisonings	100 matched controls recruited from study-subject referrals, businesses, public agencies, investigators	>30 NB tests, including: WAIS, Halstead-Reitan, MMPI-mood, questionnaires; average impairment rating; 9 years after poisoning	History of 10 OPs reported as primary cause of poisoning; methyl parathion, parathion in at least half of poisoned workers; AChE of both groups within normal limits	Paired matching on age, sex, level of education, social class, occupational class, ethnic background (Mexican)	Poisoned workers worse average impairment rating; worse on 18 of 36 NB tests; some impairment of fine motor movements; more anxiety symptoms	No information on past or current exposure of controls; no correction for multiple testing
Steenland et al., 1994	128 people from CA registry of OP-insecticide poisoning; 28% hospitalized for one night	90 friends of poisoned workers "not currently working with pesticides," 19% in agriculture	Eight NB tests from NES2 in English and Spanish, including mood scales; 1–9 years after poisoning	History of OP use; 83 also found to have significant decrease in AChE at time of poisoning; specific OPs named but limited insecticide-specific analyses because of small numbers	Poisoned workers, controls similar in mean grade level, race, preferred language, percentage of drinkers; regression to adjust for confounding	Hospitalized OP-poisoned workers significantly worse on two of 10 NB tests (continuous-performance test and digit–symbol); for all poisoned workers together, even worse performance in those with more severe poisonings; mood scales worse for tension and confusion	No information on past OP exposure of controls; no formal correction for multiple comparison
Rosenstock et al., 1991	36 men hospitalized and treated for OP poisoning in Nicaragua	25 male friends of study subjects with no prior OP poisoning; 69% with prior OP-pesticide exposure	Six of seven NB subtests from WHO battery, including BSI, CNS symptoms; Spanish-translated tests; 1–3 years after poisoning	History of OP hospitalization; no pesticide use within 3 months before testing	Matching on age, sex; testers blinded to exposure status; analysis and adjustment for premorbid intellectual functional difference in vocabulary scores	Exposed group had worse performance on five or six NB domains, more CNS symptoms (7.2 vs 4.7, $p < .01$); no difference in mood symptoms from BSI	Association strengthened by controls having prior OP pesticide exposure

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Savage and colleagues (1988) used the most comprehensive NB testing and studied a large group of agricultural workers (100 poisoned and 100 matched comparison subjects). Poisoned subjects were obtained from registries of pesticide poisonings in Colorado (1950–1976) and Texas (1960–1976). Workers were reported to have been poisoned with 10 types of OP compounds, one of which, malathion, is reviewed in this report ($n = 6$). Some of the poisonings involved more than one OP insecticide. Each OP-poisoned worker was individually matched to a comparison subject for age, sex, level of education, occupational class, socioeconomic status, race, and, in the case of Mexican Americans, ethnic background. Comparison subjects were recruited from multiple sources, including referrals from study subjects, employee rosters, and investigator solicitations. The mean elapsed time from the last poisoning to the time of testing was 9 years. No specific information on jobs or exposures at the time of testing was provided, but red-cell and plasma cholinesterase tests were performed at the time of evaluation of all subjects. Both the OP-poisoned and comparison groups were found to be well within the limits of normal red-cell and plasma AChE, so recent exposure to OP compounds was unlikely. Residue analyses were also performed for organochlorine pesticides. Although OP-poisoned workers had significantly higher mean serum concentrations of organochlorines, the analysis of covariance failed to show any significant association with organochlorine-pesticide residues or summary scores on the NB battery.

NB testing was extensive; subjects took more than 30 individual NB tests or subtests (individual tests in a test battery). Batteries included the WAIS and the expanded Halstead-Reitan battery. An average impairment rating assigned to each subject was the average of ratings (0 = better than average; 5 = severely impaired) on 11 of the Halstead-Reitan battery subtests and one WAIS subtest. The Halstead-Reitan battery included measures of intelligence, attention, cognitive functions, motor proficiency, sensory perceptual functions, aphasia and related disorders, and learning and memory. The subjects were also given the Minnesota Multiphasic Personality Inventory (MMPI). In addition, each study participant and a close relative independently completed questionnaires rating the participant's functioning regarding memory, communication, academic skills, sensory and motor abilities, various cognitive and intellectual abilities, and emotional status. Subjects also underwent a clinical neurologic examination, audiometric tests, ophthalmic tests, and electroencephalography. Examiners were blinded as to subjects' exposure status.

The poisoned subjects performed significantly worse than referents on four of five summary measures and on 18 of 34 individual tests. The differences occurred on tests of intellectual functioning, academic skills, abstraction, flexibility of thinking, and simple motor skills (speed and coordination). Of the OP-poisoned workers, 24% had Halstead-Reitan battery summary scores in the range characteristic of cerebral damage or dysfunction, compared with 12% of comparison subjects. The poisoned subjects' assessments of their own functioning found statistically significant differences in 10 of 32 aspects of language and communication, memory, cognitive functioning and perceptual functions. OP-poisoned subjects reported more difficulties in understanding speech of others ($p = 0.014$), recognizing printed or written words ($p = 0.008$), thinking of names of things ($p = 0.037$), calculating ($p = 0.009$), following instructions ($p = 0.004$), solving problems ($p = 0.036$), following directions ($p = 0.044$), performing tasks with the right hand ($p = 0.01$), and vision ($p = 0.019$). Relatives' assessment of subjects' functioning found the poisoned cohort to have more significant problems than the comparison group in four of 31 items in those same

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functions and four of 22 personality-scale items (depression, irritability, confusion, and social withdrawal). The mean scores on the MMPI were within normal limits for both groups of subjects but were significantly different on four of 13 scales that were indicative of slightly greater social anxiety and tendencies toward suspiciousness and sensitivity to social stresses. Although those results were consistent across a variety of tests, the OP-poisoned workers may have started out with somewhat lower functioning than the referents, given the group mean difference in tests of vocabulary (which is thought to be more resistant to toxic effects and to be an indicator of pre-exposure functioning). Nevertheless, paired matching and analysis were applied to a variety of factors between poisoned subjects and referents to ensure reasonable comparability and control of confounding. No correction was made for multiple testing.

The other large study (Steenland et al., 1994) evaluated 128 men listed in a California registry for pesticide poisoning and compared them with friends not currently working with pesticides. NB testing involved eight tests from the computer-administered Neurobehavioral Evaluation System (NES2). All poisoned workers had significantly worse performance on the continuous-performance test (a test measuring sustained visual attention and reaction time) and on two of five mood scales (those of tension and confusion). The more severely poisoned (hospitalized patients) performed even worse than referents on the continuous-performance test and the digit–symbol test but not on the mood scales. There was also a significant trend of worse performance on five of 10 NB tests in those who took more days off from work after poisoning. Variables related to current employment with potential pesticide exposure and years of self-reported past pesticide exposure were not found to be associated with outcomes. Insecticide-specific analyses were limited by small numbers of subjects.

Two smaller studies had similar results. Rosenstock and colleagues (1991) studied 36 men hospitalized and treated for work-related OP poisoning in a teaching hospital in Nicaragua (1986–1988). The comparison group consisted of male friends or siblings from the same community who were matched by age and had never been treated for OP poisoning. The examinations were performed in 1989 before the onset of the spraying season to reduce confounding by recent insecticide exposure. NB testing consisted of six of seven domains of the World Health Organization (WHO) core test battery. Symptoms were studied via the Brief Symptom Inventory (BSI) for mood and a 16-item CNS-symptom questionnaire covering memory, concentration, headache, and fatigue. Many of the standardized NB tests were translated into Spanish specifically for this study. The OP-poisoned workers performed significantly worse than the referents on five domains: attention, memory, visuomotor, motor, and symptoms. Individual NB tests on which performance was worse included digit vigilance (attention), digit symbol, Trails A, block design, pursuit aiming, and Santa Ana (Appendix F). There were a higher number of positive responses to the 16-item CNS-symptom questionnaire (7.2 vs 4.7, $p < 0.01$), but no other information was provided about which symptoms were affected. The poisoned workers did not differ from controls in mood symptoms on the BSI. A potential limitation of this study was the use of a comparison group in which 69% had prior exposure to insecticides. That group did not have a history of OP poisoning, but their prior exposure potentially makes it more difficult to find differences between groups. That the investigators found a difference in NB-test performance strengthens the association.

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The smallest study involved 21 Spanish-speaking men with a history of two prior OP poisonings who were referred for NB testing by attorneys who were pursuing worker-compensation claims (Reidy et al., 1992); this population is therefore a specially selected population of poisoned workers and has substantial selection bias. The committee gave little weight to this study in reaching a conclusion.

Summary and Conclusion

In summary, the strongest and largest of the studies demonstrate more NB impairment in OP-poisoned than in comparison workers (Savage et al., 1988; Steenland et al., 1994). A smaller study by Rosenstock and colleagues (1991) reported consistent findings. Results of one test used in all the studies reviewed here—digit–symbol, a test of visuomotor coordination—were shown to be abnormal in OP-poisoned workers. Most of these studies show some effects on mood (such as increased anxiety) and an increase in self-reported CNS symptoms.

Those epidemiologic studies examined the most severely exposed persons. With previously poisoned persons, there is less chance of misclassification in the exposed group. However, exposure misclassification is more likely in the comparison groups because they had substantial past insecticide exposure. That might make it harder to detect differences between exposed and comparison groups. Despite those and other limitations discussed above, there is a consistent pattern of worse performance on NB testing with past OP poisoning. What is not clear is whether long-term effects on NB function are attributable solely to the OP poisoning event or to chronic exposure, inasmuch as the poisoned workers most likely had chronic exposure as well.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between exposure to the organophosphorous insecticides under review at doses sufficient to cause poisoning (the acute cholinergic syndrome) and long-term neurobehavioral effects assessed with neurobehavioral testing and symptom reporting. The affected neurobehavioral domains include visuomotor, attention/executive functioning, motor functioning and mood symptoms.

OP Exposure and Neurobehavioral Effects Without a History of Past OP Poisoning

This section evaluates nine studies of NB effects of OP exposure without a history of past OP poisoning (Table 7.6). In most of the studies, workers were exposed for many years and so had chronic exposure. However, exposure details are sometimes sparse, and there is little information about methods of application, environmental conditions, and use of personal protective equipment or clothing.

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TABLE 7.6 Neurobehavioral Effects Without Past History of OP Poisoning

Reference	Population: Exposed	Population: Control	Health Outcomes or Test Type	OP Insecticide Exposure	Adjustment	Results	Limitations
Ames et al., 1995	45 male pesticide applicators involved in California cholinesterase-monitoring program found to have 70% decrease in red-cell AChE or 60% decrease in serum AChE from baseline in records from 1985, 1988, 1989, but with no evidence of frank poisoning	90 male friends who had no history of past pesticide poisoning, past cholinesterase inhibition, or current pesticide exposure; no information on other past OP exposure, but 19% in agriculture	Eight computerized NB tests from NES: mood scales, finger tapping, sustained attention, hand–eye coordination, simple-reaction time, digit–symbol, pattern memory, serial-digit learning; noncomputerized Santa Ana dexterity test, pursuit aiming; regression coefficients to compare controls, exposed provided from regression models	History of use of OP insecticides; no information on specifics, but significant enough to lower AChE enough to cause removal from work	Used multiple linear-regression models to adjust for age, grade level, language of test (Spanish or English) for NB testing For motor coordination tests, models involving ethnicity, age, grade level, height, weight used; no difference in alcoholic drinks, cups of coffee, hours of sleep before testing	No significant differences between referents and exposed on NB tests (except serial-digit performance, in which exposed performed better than referents)	Authors state that workers expected not to have current exposure, but basis for expectation not clear; possible misclassification error because referent group may have had significant OP exposure
Stephens et al., 1995	146 sheep farmers exposed to OP in course of sheep dipping; no dipping; in prior 2 months; contact by random-number selection; 69% response rate	143 nonexposed rural quarry workers from same area, response rate 35%	Eight computer-administered NB tests, General Health Questionnaire, Subjective Memory Questionnaire	Retrospective exposure questionnaire; dose index (average number sheep × number dips/year × number of years using OP insecticides); urine sample for dialkylphosphates to confirm lack of exposure during previuos 48 hours	Age, lifetime alcohol, smoking, computer familiarity, educational level, time of day of testing, first language; key ones included as covariates in multivariate analysis	Farmers significantly worse in tests of motor, visuomotor skills, cognition (simple-reaction time, digit–symbol, syntactic reasoning); dose–effect relationship for syntactic reasoning; farmers more symptomatic on General Health	Specific symptoms not reported; number of years of chronic exposure not reported

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Reference	Population: Exposed	Population: Control	Health Outcomes or Test Type	OP Insecticide Exposure	Adjustment	Results	Limitations
Fiedler et al., 1997	57 white male New Jersey fruit-tree farmers (pesticide applicators); initial response rate, 39%; no history of pesticide poisoning	23 volunteer blueberry–cranberry growers expected to have little or no exposure to pesticides (but other growers do have OP exposure); initial response rate, 14%); 20 male volunteer hardware-store owners; initial response rate, 8%	15 NB tests, including WRAT-R to estimate premorbid intellectual ability, MMPI-2	Detailed exposure interview to construct lifetime exposure metric; red-cell AchE; potentially low exposures over long time because farmers were owners and family members	Covariance analysis to adjust for confounders; referent group significantly more years of education, better reading test (WRAT); reading-test score used as covariate in analyses of each NB variable	All red-cell AChE normal (but not compared with subjects' baseline, so acute OP effects less likely); simple-reaction time significantly longer in exposed than in referent and in high than low exposure; in regression analysis, exposure not correlated with reaction time	May have been some misclassification error because OP-pesticide exposure may have occurred in referent group of blueberry–cranberry growers; potential selection bias (farmers with pesticide problems did not want to volunteer)
Bazylewicz-Walczak et al., 1999	26 women performing planting jobs in greenhouses and using OPs but without history of earlier poisoning	25 women not exposed to neurotoxins; employed in kitchens, administrative jobs	Six NB tests (Polish adaptation of WHO NCTB), two symptom questionnaires (POMS, FSSQ); performed before, after pesticide application	OPs include dichlorvos, metamidophos, methidathion, pirimiphos-methyl; some carbamates, synthetic pyrethroids, dithiocarbamates; predominantly OPs measured on clothing, skin washes, air sampling during application midseason; dose "low," or below 0.010 % of toxic dose; also carbamates, synthetic pyrethroids, dithiocarbamates	Groups similar in sex, age, education, residence, comparison of group characteristics (by ANOVA and chi-square tests) did not reveal significant differences between exposed, control groups	No significant changes over spraying season except increased errors in aiming test; long-term effects of exposure ("group factor"); OP-exposed had slower simple reaction and lower hand-movement efficiency (aiming), more mood (anxiety, depression, fatigue), more CNS symptoms than referents	Limited number of NB tests, sparse detail on some aspects of methods

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Reference	Population: Exposed	Population: Control	Health Outcomes or Test Type	OP Insecticide Exposure	Adjustment	Results	Limitations
Steenland et al., 2000	191 termiticide applicators from North Carolina registry, including 105 current applicators and eight formerly poisoned; median exposure, 1.8 years (1987–1997)	189 nonexposed referents (106 friends of exposed, 83 state employees)	Nine NB tests: seven from NES, Trails A and B; 24-item symptom questionnaire	Chlorpyrifos, some chlordane (1987–1988)	Regression: age, race, education, current smoking, body-mass index	Past exposure only group: one NB test significant (grooved pegboard for dominant hand); 12 of 24 symptoms more prevalent than in referents	Possible selection bias due to inability to locate majority of exposed population; exposed, referents had occupational history of solvent exposure
London et al., 1997	163 (from original pool of 231) spray men selected from deciduous fruit farms in South Africa	84 nonspraying male laborers from farms, matched on age, educational status	Five NB tests based on WHO NCTB without POMS, FSSQ; other information-processing tests for populations with little education	Long-term exposure calculated with job-exposure matrix; recent exposure assessed with history, plasma cholinesterase within 10 days of NB testing	Multiple linear, logistic regression used for long-term outcomes, exposure, factors of age, education, past history of pesticide poisoning, recent OP exposure, residential exposure, number of years of exposure	Multiple regression models showed small yet significant correlation between lifetime occupational OP exposure and pursuit aiming, Santa Ana Test, one of 21 tests of information processing	NB data present on all subjects, not cases and controls separately; current exposure; cannot separate long-term from short-term effects; no clear comparison of referents or exposed; high alcohol use in all
Gomes et al., 1998	226 migrant farm workers who had worked for at least 2 years in United Arab Emirates; 92 unmatched new farm workers who had worked in farming in another country for at least 2 years	226 referents never occupationally exposed to pesticides, never handled pesticides for domestic use; employed as domestic workers or in shops, offices, or industry	Two NB tests: digit–symbol, aiming; questionnaire: 30-day-recall symptom checklist	Farm workers lived on farms, did tilling, pesticide spraying, harvesting; red-cell AChE measure (timing related to spraying not known); data on duration of exposure collected but not run in regression analysis	Referents matched by age, nationality	Farm workers had statistically more symptoms of dizziness, headache, restlessness, sleeplessness than referents and did worse on digit–symbol test, aiming test; on regression analysis, type of job was significant predictor of symptoms; farm work also predicted low scores on symbol test and aiming test, lower AChE activity; AChE predicted blurred vision	Current exposure; cannot separate long-term from short-term effects

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Reference	Population: Exposed	Population: Control	Health Outcomes or Test Type	OP Insecticide Exposure	Adjustment	Results	Limitations
Daniell et al., 1992	49 volunteer male apple orchard pesticide applicators from Washington State; three had previous episodes of pesticide poisoning	40 volunteer male slaughterhouse workers; 68% currently nonexposed referent subjects had prior work picking or trimming crops, 27% used pesticides in past	Five NB tests from NES in English, Spanish; computer-administered.	OP pesticides, particularly azinphos-methyl; AChE measured	Stratified by language preference because of differences in educational level, other factors	No important differences between applicators and referents were found on preseason NB tests (when language preference considered); across-season changes resulted in no differences except decrease in digit–symbol test (in Spanish-preference group); no correlation of any NB results with AChE	No vocabulary or other tests to establish baseline CNS functioning; small comparison groups could contribute to difficulties in finding differences
Rodnitsky et al., 1975	23 exposed men: 12 farmers who personally apply OP to crops or animals, 11 commercial pesticide applicators; no information on how selected, must have used an OP compound within 2 weeks of testing date	23 farmers, matched for age, educational background; tested before spraying season or not involved in pesticide handling during spraying season	Five tests: memory tested by verbal-recall task, vigilance by simple-reaction time, signal-processing time, sentence-repetition subtest of Multilingual Aphasia Examination, proprioception (use of spring-loaded button, forefinger)	Regular use of OP insecticides, but many used other types as well (not described) Red-cell and plasma AChE measured, but timing not reported; no comparison with baseline; comparison of group means	Referents matched for age, educational level	Exposed subjects performed as well as referent subjects on five tests; mean plasma ChE of exposed group lower than that of referent group but not below “normal”	Study of acute effects of pesticide exposure, particularly given relative inhibition of AChE in exposed group; no information or adjustment for other possible differences between referent and exposed, such as language or intelligence level

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One epidemiologic study selected its exposed population on the basis of a past finding of a decrease in AChE during 3 different years. Ames and colleagues (1995) studied 45 pesticide applicators that had participated in the California medical–surveillance program for OP insecticides. All had been found to have substantial declines in AChE, requiring removal from work, even though they had no evidence of frank poisoning (the acute cholinergic syndrome). California law requires removal of a worker when cholinesterase values have fallen 30% or more for red blood cell cholinesterase or 40% or more for plasma cholinesterase from pre-exposure baseline values. The decreases in AChE were noted in medical supervision records for 1985, 1988, and 1989. Duration of exposure was not reported, but workers' records covered a 4-year period, which implied chronic, if intermittent, exposure. The study stated that none of the subjects was expected to have current cholinesterase inhibition.

The study was part of a larger study of poisoned subjects and had the same comparison group as a previously reported study (Steenland et al., 1994). Each exposed subject was asked to select a friend of comparable age (a "comparison subject;" $n = 90$) not currently exposed to pesticides and without a history of OP-pesticide poisoning or a past decrease in AChE. Little information, however, was provided about the previous jobs or exposures of the comparison subjects, although 19% were reported to have had "current employment in agriculture." Outcome measures consisted of results of eight NB tests from the computer-administered NES2 (Ames et al., 1995) mood scales, finger-tapping, sustained attention (continuous-performance tests), hand–eye coordination, simple reaction time, digit–symbol, pattern memory, and serial–digit learning. There were also two noncomputerized tests: the Santa Ana dexterity test and the pursuit aiming test (Appendix F).

The AChE-inhibited subjects on the average were older than the comparison group and had lower educational achievement (which may have decreased test performance) and had slightly higher body-mass index, were less likely to be current smokers or drinkers, and drank alcohol less often before testing (which could have improved test performance). Those factors were included in multiple linear-regression models to determine whether the exposed differed from the comparison population with respect to neurologic measures. When the values of the adjusted regression coefficients were examined, the AChE-inhibited subjects were not found to have worse performance on any of the NB measures than the comparison group. The AChE-inhibited group performed statistically better than the comparison group on serial-digit performance. The study did not administer a symptom questionnaire, but it did include a "mood scale" as part of the NES battery. No significant differences were found.

In summary, Ames and colleagues (1995) found no evidence of an association between moderate OP insecticide or *n*-methyl carbamate exposure, as reflected by prior blood AChE inhibition and effects on NB tests, including mood scales, in the absence of frank poisoning. However, the identification of statistical differences between exposed and comparison groups was rendered more difficult by the fact that almost one-fifth of the comparison group worked in agriculture and thus might have been misclassified.

In other studies of workers handling OP insecticides, discussed below, the exposed groups were made up largely of people who applied pesticides to plants or farm animals. In some studies, the evaluations occurred while the workers were still using pesticides. That made it more difficult to discern short- and long-term effects. Many of the studies used

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comparison groups with past exposure to farming or pesticides (Cole et al., 1997; Daniell et al., 1992; Fiedler et al., 1997; London et al., 1997; Rodnitzky et al., 1975), which made it more difficult to find differences between the exposed and control groups. All the studies administered NB tests. None assessed the clinical significance of an effect, namely, whether the effect was associated with significantly lower functional activity. Studies also did not attempt to correlate NB test results and symptom findings.

A large study (Stephens et al., 1995) evaluated 146 sheep farmers who were exposed to OP insecticides in the course of sheep dipping and, for comparison, 143 rural quarry workers. The farmers were recruited from registration lists of the Wool Marketing Board for three regions of England and Wales, and the response rate was 69%. The study indicated that the farmers' OP exposure was chronic, but it did not specify the number of years of exposure. The effects of recent insecticide exposure were eliminated or reduced by using sheep farmers who had not performed sheep dipping for 2 months before testing. Farmers also provided urine samples to test for metabolite (dialkylphosphates) to confirm further the lack of exposure to OPs during the previous 48 hours. Those exclusions were designed to focus on long-term, rather than short-term, effects. Study participants completed the General Health Questionnaire (30-item version) to screen for "vulnerability to psychiatric disorder," the Subjective Memory Questionnaire (43 items) to measure subjects' own assessment of memory, a retrospective exposure questionnaire, and eight computer-administered NB tests. The farmers scored significantly worse in three tests of motor skills (that is, simple reaction time, visuomotor skills, digit–symbol substitution), and cognition (that is, syntactic reasoning). The authors note that these effects "are subtle in nature, and … unlikely to be manifest as clinical symptoms." On the basis of the self-reported exposure data, five dose groups were constructed, and a significant effect of dose group was observed for the syntactic reasoning test ($F = 5.54$, $p \leq 0.0001$) with ANCOVA. The adjusted mean scores on the Subjective Memory Questionnaire were not significantly different between the groups. The OR calculated from the General Health Questionnaire (in which "caseness" was defined as a report of at least five symptoms) was 1.5 (95% CI = 1.31–1.69), indicating that the odds that farmers would report at least five psychiatric symptoms were 50% greater than those of comparison subjects. Further details on types of symptoms are not provided, and symptom findings were not dose-related. The authors reported being unable to rule out the role of social and economic factors in development of psychiatric symptoms.

In another study, Fiedler and co-workers (1997) studied 57 self-employed fruit-tree farmers who applied pesticides; the comparison group consisted of 23 blueberry–cranberry growers thought to have little or no exposure and 20 hardware-store owners. Researchers had found the applicators on a list of New Jersey-licensed pesticide applicators and contacted them by mail. Subjects were given 15 NB tests and the MMPI-2 to assess psychiatric and emotional states. Testing was conducted during the nonspraying season. Red-cell concentrations of AChE were within "normal laboratory ranges" in both exposed and nonexposed, but baseline (pre-exposure) concentrations were not available. Although OP-insecticide exposure might have occurred at the time of evaluation, the normal AChE readings suggest that large, recent OP exposure was unlikely. Simple-reaction time was found to be significantly longer in the exposed than in the comparison group and in the high-exposure than in the low-exposure group. However, the calculated exposure metric was not correlated with reaction time, so no dose–response relationship was shown. The study was relatively small, and the lack of significance on more of the NB tests may be related to that.

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There also may have been some misclassification error: pesticide exposure may have occurred in the comparison group of blueberry–cranberry growers, who may also have used insecticides. The authors speculated that the detection of simple-reaction time as the only abnormal finding might have been a chance positive result of multiple testing.

Bazylewicz-Walczak and co-workers (1999) studied 26 women who performed planting jobs in greenhouses. They used OP insecticides and other pesticides (mostly OPs, but also carbamates, synthetic pyrethroids, and dithiocarbamates) but had no history of past poisoning. The greenhouse workers were compared with 25 women who were employed in kitchens and administrative jobs and had no exposure to insecticides or solvents. Subjects were tested before the spraying season (probably a no-exposure period) and 1 month after the 3-month spraying season. Outcome measures included results of six tests from the WHO Neurobehavioral Core Test Battery (NCTB) and two symptom questionnaires (POMS and the Finnish Subjective Symptoms Questionnaire, FSSQ). Environmental sampling at peak OP-insecticide use estimated that the typical exposure was "low" or below 0.01% of WHO's toxic dose. Investigators found little change associated with recent exposure during the spraying season except for a significant increase in errors on the aiming test (visuomotor coordination). Analysis of preseason data for what was termed the group effect (comparing exposed and control groups with ANCOVA) indicated possible long-term effects of exposure: a significantly longer simple-reaction time and slower hand-movement efficiency on the aiming test. The exposed group, before the spraying season, also reported significantly more anxiety, depression, and fatigue or inertia on the POMS and more complaints of "absent-mindedness" ($p = 0.10$) and neurologic symptoms ($p = 0.10$) than did referents. Neurologic symptoms were not specified. The limitations of this study were small sample size, limited number of NB tests, and sparse detail on some aspects of methodology.

Steenland and colleagues (2000) conducted a cross-sectional survey of 191 current or former termiticide applicators exposed predominantly to chlorpyrifos and 189 nonexposed controls. The applicators that agreed to participate amounted to fewer than half the eligible applicators. One-third were former applicators; they had not worked with pesticides in the current year (1998). Exposure assessment was based on questionnaire response and job history and was supplemented with measurements of a urinary metabolite of chlorpyrifos. Regression analyses adjusted for age, race, education, and current smoking. Applicators had worked a median of 1.8 years in applying termiticides. (Further details of the study were given earlier in this chapter in the section on peripheral neuropathy.) The investigators tested workers on the NES and two NB tests of eye–hand coordination. The former applicators (n= 63) performed significantly worse on the grooved-pegboard test for the dominant hand (a test of motor skills) but not on other NB tests. Formerly exposed applicators also had significantly increased prevalence of 12 of 24 symptoms, but the report does not specify which ones. A major weakness in the study was the potential for selection bias due to nonparticipation during recruitment. Another limitation was potential confounding by occupational exposure to solvents in exposed and comparison groups.

Two other studies demonstrated small positive findings on NB testing but faced challenges in performing assessments in populations with low literacy. London and colleagues (1997) evaluated 163 men who used pesticides on fruit farms in South Africa and 84 nonspraying laborers who also worked on the farms and were matched for age and educational status. The study used the WHO NCTB screening subtests (except for POMS and the Subjective Symptoms Questionnaire, which were excluded because previous studies

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established poorer performance in workers who had little education). The researchers also used other information-processing tests, which were deemed more appropriate for testing people who had little education. Long-term exposure was calculated with a job–exposure matrix. According to a multiple-regression model, cumulative lifetime occupational exposure was significantly associated with a reduction in the number of correct trials on pursuit aiming and on the Santa Ana test of the nondominant arm. Because workers had current exposure, this study could not distinguish between short-term and long-term effects of OP insecticides.

Gomes and co-workers (1998) compared 226 farm workers in the United Arab Emirates with 226 referents employed in shops and offices, in industry, or as domestic helpers. The comparison subjects were matched for age and nationality and had never been occupationally exposed to pesticides or handled pesticides for domestic use. Outcome measures included the results of a 30-day symptom-recall checklist and two NB tests, the digit–symbol and pursuit aiming. Red-cell AChE was measured at the time of NB testing. The exposed group continued farm work and handling of pesticides during the evaluations. Farm workers had significantly more symptoms of dizziness, headache, restlessness, and sleeplessness than referents, and did significantly worse on the digit–symbol and aiming tests. On regression analysis, farm work was a significant predictor of weakness, abdominal pain, blurred vision, muscular pain, restlessness, and, to a smaller extent, sleeplessness. Farm work was also predictive of low scores on digit–symbol and aiming tests and of low AChE. AChE decrease also significantly predicted weakness and blurred vision, known symptoms of cholinergic excess. Although data on duration of exposure ("period of service") were collected, that was not reported as a factor in the regression analysis. Given that subjects were continually working and exposed during the study period and that the findings were correlated with a decrease in AChE, it is highly probable that the abnormal NB and symptom findings were related to recent exposure to OP insecticides. It is therefore difficult to separate long-term effects from short-term effects.

Studies by Daniell and co-workers (1992) and Rodnitsky and colleagues (1975) found no NB abnormalities. Daniell and co-workers studied 49 male orchard pesticide applicators in Washington State. They were compared with 40 male slaughterhouse workers (68% had worked in picking or trimming crops, and 27% had used pesticides in the past). The applicators used OP pesticides, mostly azinphos-methyl. NB testing consisted of five computer-administered tests from the NES delivered in English or Spanish. Evaluations were performed before and after spraying season. It was necessary to stratify the analyses by language preference because of differences in educational level between Spanish-speaking and English-speaking subjects. There were no statistically significant differences between pesticide applicators and referents on the preseason NB-test results, which would have reflected long-term exposures.

The study by Rodnitsky and colleagues (1975) was also small, comparing 23 men who applied pesticides with 23 farmers who were not handling pesticides during the time of the evaluation. The exposed population had used an OP insecticide within 2 weeks of the evaluation. Five NB tests were performed. Referents were matched for age and educational level. Red-cell AChE and plasma AChE were measured, but no information was provided as to the timing of the measurement, nor was there comparison with individual baseline values. Group AChE means were compared, and the plasma AChE of the exposed group was lower than that of the comparison group but not below normal. There were no significant

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differences between exposed and comparison subjects in results of five NB tests. Given that OP-insecticide exposure occurred at least within 2 weeks of testing, this study was focused on detecting effects of recent than of past OP exposure. Small samples, potential pesticide exposure among the referents, and the use of relatively few NB tests may have compromised the ability of these two studies to detect significant NB effects of OP pesticides.

Kilburn (1999) studied people exposed to chlorpyrifos in the indoor setting who had been referred to a testing center. The study included people with past but no current exposures, but the study results are difficult to interpret because they represent a highly selected clinic sample or case series compared with historical referents.

Summary and Conclusion

In summary, four studies were evaluated to draw conclusions about long-term NB effects in persons handling OP insecticides but with no history of earlier OP poisoning. One found no adverse NB effects on the basis of test results in an exposed group with the best documentation of exposure to OP insecticides (Ames et al., 1995). However, the comparison was with friends of the exposed subjects, on whom little exposure history is available and 19% of whom had worked in agriculture, and the possibility of past insecticide or other exposures in the comparison group may have diminished the chances of finding significant differences between exposed people and referents. Another study compared an exposed group of sheep dippers with a large, objectively chosen comparison group that had no pesticide or chemical exposure (Stephens et al., 1995). With control of confounding factors, the study found significant performance decrements in three NB tests of visuomotor (digit–symbol), motor (simple-reaction time), and cognitive (syntactic reasoning) functioning and a dose–response relationship for the latter. The clinical impact of these findings was described by the study authors as subtle and unlikely to be manifest as symptoms. The exposed group was more likely to report psychiatric symptoms, but the authors could not rule out the impact of social and economic factors on symptom reporting.

Several other studies had some positive findings, but also limitations. The study by Fiedler and colleagues (1997) found that the exposed group had significantly worse performance on a single test (simple-reaction time), but there was no dose–response relationship, and there was potential misclassification error in the comparison group; the authors speculated that the positive finding was by chance. Bazylewicz-Walczak and colleagues (1999) found abnormalities on simple-reaction time and on the aiming test, but measured performance on only six NB tests and was sparse on some aspects of methodology. A population-based study of Gulf War veterans (discussed earlier in this chapter) found dizziness and balance symptoms related to pesticide handling, but there was no dose–response relationship or NB testing (Cherry et al., 2001a).

Some committee members believed that the evidence for long-term neurobehavioral effects reached the level of limited/suggestive because they viewed the study by Stephens and colleagues (1995) as a high-quality study with positive findings consistent with findings from two smaller studies of lesser quality (Fiedler and colleagues, 1997; Bazylewicz-Walczak et al, 1999). Other committee members believed that the evidence was inadequate/insufficient as the neurobehavioral test findings were too subtle to reach the level of clinical significance, and only one of the NB test findings (i.e., syntactic reasoning, a test of cognition) showed a dose–response relationship. The nature of the symptom findings from a separate questionnaire were not reported. The findings from the two smaller studies

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were not sufficiently robust to reinforce those from Stephens and colleagues. Therefore, the committee was unable to reach consensus on a conclusion regarding exposure to organophosphorous insecticides under review at doses insufficient to cause poisoning (the acute cholinergic syndrome) and long-term neurobehavioral effects.

SOLVENTS AND NEUROBEHAVIORAL EFFECTS

Exposure to high concentrations of solvents is known to produce short-term NB effects (Chapter 4), including fatigue and impairment of memory and concentration (Spencer et al., 2000). The question relevant to Gulf War veterans is whether exposure to relevant solvents is associated with long-term NB effects that persist after exposure ceases.[9]

This section evaluates the evidence of long-term NB effects—as measured by symptom reporting or NB test performance—as a result of exposure to the solvents of interest to the committee. The committee had previously established three inclusion criteria for its evaluation of the occupational insecticide and solvent literature regarding NB effects discussed earlier in the chapter. It is important to remember that one of the criteria noted that the study must include an exposure-free interval of weeks to months before testing of study subjects or a subset of subjects (that is, workers with only past exposure). The purpose of that criterion is to distinguish between long-term (persistent) and short-term effects of solvent exposure. The criterion turned out to be very restrictive as the vast majority of the more than 300 solvent studies in the peer-reviewed literature focus on workers with *both* current and past exposure. For reasons explained earlier, studies examining current and past exposures together are not able to discriminate between short-term and long-term effects. Applying the three inclusion criteria resulted in the committee's evaluating seven occupational studies of NB effects.

As background, it is important to acknowledge that the solvent literature refers to a solvent-induced condition termed "chronic toxic encephalopathy," often described as impairment of cognitive performance. One of the earliest studies of this putative condition linked it to premature retirement of solvent-exposed workers in Scandinavia (Mikkelsen, 1980). The committee evaluated studies of chronic toxic encephalopathy (and similarly named syndromes) if they reported results on its constituent symptoms or NB test performance (for comparability with other studies) and met the committee's inclusion criteria. One of those studies (Mikkelsen et al., 1988) figured prominently in the committee's conclusions of limited/suggestive evidence of an NB effect. The committee did not evaluate the evidence of chronic toxic encephalopathy or similar clinical syndromes, because of the lack of uniform application of diagnostic criteria (Rom, 1998; Spencer et al., 2000; van der Hoek et al., 2000). The committee's approach—to break down putative syndromes into constituent symptoms and effects on performance—is analogous to that taken by Gulf War researchers investigating NB impairment in the absence of a clearly defined syndrome (Appendix A).

[9]The effects of prolonged toluene abuse or intoxication (extremely high exposure over the course of 1 year) persist after exposure ceases (according to case studies; also see Chapter 4).

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Epidemiologic Studies of Exposure to Solvents

There are seven studies discussed in this section (Table 7.7). Mikkelsen and colleagues (1988) conducted comprehensive clinical evaluations of 85 house painters and 85 bricklayers.[10] Subjects were recruited by random sampling from local union memberships; a supplementary sample was obtained by random stratified sampling based on symptom reporting in a prerecruitment questionnaire. Participation rates were moderately high (61–75% of those approached). The painters had been in their trade for at least 5 years (mean, 32 years). Half the painters (49%) reported no solvent exposure for at least a year, and only eight reported exposure within 2 days of evaluation. The study included clinical evaluations, 14 NB tests, and a symptom questionnaire. Because it did not separately list or describe the findings from the symptom questionnaire, such results were not included in the committee's evaluation. A solvent-exposure index was devised by the investigators to reflect the number of years in a particular occupation (house painter, ship painter, industrial painter, and silk-screen painter) weighted by the average daily use of solvents. The adjusted analyses of the relation between solvent exposure and NB tests used age, alcohol use, educational achievement, verbal IQ, the presence of atherosclerosis, and history of neurologic disease as covariates. The results showed that painters had a significantly lower score than bricklayers on two NB tests: the digit–symbol and the block design (time per design, as opposed to correct number, which was nonsignificant). Performance on the digit–symbol test was significantly related to exposure: the most highly exposed performed worst. There was a marginally significant exposure-related trend ($p = 0.066$) for a summary measure based on nine of 14 NB tests. A separate analysis of current vs formerly exposed workers was not conducted, but the overwhelming majority of the workers did not report exposure within 2 days of the evaluation, and 49% had not been exposed for a year or more. In summary, the study found that solvent exposure adversely affected tests of visuomotor and visuospatial skills. The findings for visuomotor and overall NB function were dose-dependent.

One of the major aims of the Mikkelsen et al. (1988) study was to relate solvent exposure to a diagnostic category that the authors termed dementia. A psychologist scored each subject's degree of dementia. The authors acknowledge that there were no a priori criteria for this category, and it was based on the psychologist's clinical assessment. Nevertheless, it is important to point out that an appendix to the study described an analysis to isolate the determinants of the psychologist's dementia score. It found that the clinical assessment of dementia was influenced primarily by NB test performance (85% of the variance) and secondarily by symptom reporting and other clinical information. In addition, the study found that subjects with "suspected," "mild," or "more than mild" dementia reported significantly more symptoms of "mental impairment" and performed significantly less well on NB tests than subjects judged to have no dementia and with adjustment for age and verbal ability. The risk of dementia was found to increase with cumulative exposure and was not associated with recent exposure (during the preceding week, month, or 3 months). The study also attempted to assign functional significance to the dementia score. When differences in age and verbal ability were adjusted for, people with greater degrees of dementia were less likely to be employed (the OR for not being professionally active was 1.2 for "suspected dementia," 2.04 for "mild dementia," and 21 for "more than mild dementia").

[10]Bricklayers are not likely to have been exposed to solvents.

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TABLE 7.7 Neurobehavioral Effects and Solvent Exposure

Reference	Exposed Population	Control Population	Health Outcomes or Test Type	Solvent Exposure	Adjustments	Results	Limitations
Mikkelsen et al., 1988	85 painters	85 bricklayers	14 NB tests, neurologic examination, symptom questionnaire	Paint, solvents; exposure index	Age, alcohol, education, verbal IQ, atherosclerosis, neurologic disease, word blindness	Decrease in performance in block design, symbol digit; latter related to degree of exposure	Symptom results not reported separately; clinical assessment not specified
Hannien et al., 1991	21 members of group of monozygotic twins; exposed twins	21 members of group of monozygotic twins; nonexposed twins	13 NB tests, including WAIS, POMS, personality test	Solvents, glues by work history; exposure index	Exposure index	Exposure associated with poorer performance on associative learning, digit span, block design, POMS symptom of absentmindedness	Of exposed twins, 13 of 21 with only prior exposure; only one comparison between current and past exposures on many NB tests
Parkinson et al., 1990	567 female microelectronics workers at plant in Pennsylvania	Different categories of exposure in same plant	Nine "neurologic" symptoms, Hopkins symptom checklist for depression, eight "somatic" symptoms, five NB tests	Solvent exposure in five categories, including two with only past exposure	Seven risk factors, including age, smoking, alcohol intake, obesity, medical disease	Groups with only past exposure had significantly more headaches, weakness or fatigue, rashes, abdominal pain; no difference on NB tests	
Stollery, 1996	Two groups of women: eight accidentally exposed to toluene, other aliphatic hydrocarbons, 10 with past chronic exposure in same factory	10 workers in the factory, but in packing department	Four NB tests	Toluene, other aliphatic hydrocarbons in acute spill and with past chronic exposure; study 3 years after initial study (Stollery and Flindt, 1988)	Age, duration of employment	Syntactic, semantic reasoning worse in those with acute intoxication	

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Reference	Exposed Population	Control Population	Health Outcomes or Test Type	Solvent Exposure	Adjustments	Results	Limitations
Daniell et al., 1993	100 car body repair workers: 29 with past exposure, 71 currently exposed	24 never-exposed car body repair workers	11 tests from NES, symptom questionnaire, after-the-fact outlier score	Paints, solvents; exposure in four groups	Age, education, vocabulary score, alcohol use	Past-exposure group had more symptoms, including lightheadedness, tiredness, irritability, lack of coordination; NES findings nonsignificant	
Lundberg et al., 1995	135 house painters born 1925–1945, in local unions	71 carpenters born 1925–1945, in local unions	12 NB tests, neurologic and psychiatric symptoms	Paint, solvents; exposure index	Age, alcohol, reading and writing abilities, vocational training, handedness	Only block design was worse in painters than carpenters and was dose-dependent; subset with only past exposure not significantly different from currently exposed	Limited analysis of past-only exposure subset
Daniell et al., 1999	89 retired solvent-exposed workers 62–74 years old: 67 painters, 22 aerospace workers.	127 retired carpenters	21 NB tests, 25 symptoms, Beck depression inventory, psychiatric interview, after-the-fact outlier score	Paints, solvents; weighted by exposure level	Age, education, race, vocabulary score, alcohol	Painters significantly worse on motor score; subgroup of moderately to highly exposed aerospace workers significantly worse on visuomotor speed, motor; painters had significantly higher symptom scores, including fatigue, difficulty in concentrating; painters had more depression symptoms but not diagnoses; painters had higher rates of alcohol use; painters, aerospace workers with medium or high exposure had higher outlier scores, indicating clinical significance	

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Hanninen and co-workers (1991) investigated previous exposure to organic solvents and NB-test performance in 21 twins discordant for solvent exposure during adult life. The authors used the Finnish Twin Registry that had information on 4300 monozygotic twins. They identified 30 pairs with discordant exposures, but interviews indicated that only 21 twin pairs were truly discordant. An exposure index was constructed from work history; the most common occupations were in painting or gluing (the most commonly used solvents were reported to be aliphatic hydrocarbon mixtures, toluene, and xylene). The median duration of exposure was 13 years, but the degree of exposure during that time was only one-third of the Swedish standard, and this led the investigators to conclude that the overall exposure was low to medium. An additional 28 pairs of twins were included as reference pairs. Of the 28 pairs, 21 were discordant for exposure and 13 of the 21 (62%) had been exposed only in the past. The NB testing battery consisted of 13 tests, including the POMS and personality. The analysis was adjusted for the degree of exposure in the discordant twin. The study found that exposure to solvents was associated with poorer performance on the associative-learning, digit-span, and block-design tests. Absentmindedness was the only symptom on the POMS that was significantly more common among exposed twins. Only one analysis compared formerly exposed with currently exposed twins: using a composite measure of nine NB tests, it was found that previously exposed twins performed somewhat better than currently exposed twins, but the difference did not reach statistical significance, and performance was still poorer than that of the reference twins. There was, however, no direct statistical comparison between the formerly exposed and the reference twins, but only between the formerly and currently exposed twins. The overall conclusion of the study was that solvent exposure affected primarily measures of attention and concentration and of visuospatial relations.

Lundberg and colleagues (1995) investigated 135 house painters and 71 carpenters born in 1925–1945.[11] Both groups were affiliated with local trade unions, and most subjects were retired or had left active employment because of disability. The painters had a history of long-term exposure to organic solvents and thus constituted the exposed group. About half the painters (66) had no exposure within a year of evaluation, and this indicates an exposure-free interval. The investigators administered 12 NB tests and a symptom questionnaire. The analysis was adjusted for age, alcohol use, reading and writing abilities, vocational training, and handedness. Because the analysis of symptom questionnaires was not stratified by past vs current exposure, the results were not evaluated by the committee. Of the NB-test results, only block-design performance was worse in painters than in carpenters. The finding was dose-dependent, with larger effects at higher cumulative exposure. However, it is not clear from the publication whether the authors conducted a direct comparison of formerly exposed and reference workers (carpenters). The overall study conclusion was that chronic exposure to solvents was associated with poorer performance on a visuomotor task.

Parkinson and colleagues (1990) studied 567 female microelectronics workers in a Pennsylvania plant. Exposures at the plant included alcohol, acetone, xylene, trichloroethylene, trichloroethane, tetrachloroethylene, benzene, and dichlorobenzene. None of the workers used a respirator. The cohort was divided into five exposure groups the basis of analysis of self-report questionnaires, structured interviews, and a plant tour. Two of the

[11]Another study of the same cohort by Michelsen and Lundberg (1996) is not included here, because there was no analysis of the subset of workers with only past exposure.

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five groups had only past exposures: not exposed in the preceding year (n = 173) and exposed in the preceding year but not within 2 weeks of interview (n = 60). The mean tenure in the current job was 2.5 years for the entire cohort. The two groups with only past exposure were significantly more likely than the never-exposed plant workers (n = 73) to report headaches (OR = 2.6), weakness or fatigue (OR = 2.97), rashes (OR = 2.56), and abdominal pain (OR = 2.59). The results were adjusted for seven risk factors as indicted in Table 7.7.

Stollery (1996) investigated the long-term effects of exposure to organic solvents in a followup study of women working in a tennis-ball factory who were exposed to high concentrations of toluene and other aliphatic hydrocarbons as a result of a ventilation accident; atmospheric monitoring was not conducted at the time of the accident, but solvents then used were toluene and SPB-7, a proprietary solvent containing hexane, heptane, octane, and nonane. Solvent exposure occurred over a 3-day period apparently because of failure of the ventilation system. The most severely exposed workers lost consciousness, experienced headaches, felt intoxicated, and had occasional vomiting. Following the problem with the ventilation, the factory underwent major renovations to control workplace contaminants, including the discontinuation of toluene use and its replacement with a water-soluble adhesive. A study, conducted 8 months after the accident, compared seven of the 12 most severely affected women with eight women who had prior chronic exposure in the same factory and to the same solvents but were not near the accident site (Stollery and Flindt, 1988). A group of 10 women who worked in the packing department of the factory were included as a second comparison group because they were not exposed to organic solvents. All three groups were matched on age and duration of employment (9 years). The acute-exposure group also had chronic exposure before the accident. No environmental monitoring was available before or during the accident. After 2–8 months, the acutely exposed women performed worse on paired associates, a word-list learning task, and the Brown–Peterson task of word recall than their peers who regularly worked with the solvents and the nonexposed workers. Three years later, the same investigators evaluated the women and included a few who had not been originally studied (Stollery, 1996). Only syntactic and semantic reasoning differed between the group with previous acute exposure and two other groups (chronic exposure and nonexposed). The earlier study showed diminished performance in memory tasks, but the long-term effects observed in the later study (3 years after the accident) were characterized as a slowing in verbal reasoning with no loss of accuracy. The three groups of women were similar in memory performance. The researchers concluded that slowed verbal reasoning was a long-term effect of the acute intoxication.

Daniell and colleagues (1993) studied 124 car-body repair workers who were exposed to solvents through spray painting or a combination of spray painting and body repair. The sample was divided into four groups: never painted (n = 24), past exposure (n = 29, over 5.6 years average duration), and two groups with current exposure—medium exposure (n = 32) and high exposure (n = 39). Study subjects were given 11 tests from the NES and a symptom questionnaire that included nervous-system symptoms. The study also developed a measure to assess the relative functional significance of NB effects. The findings presented here focus only on the outcomes in the previously exposed painters. They reported more symptoms (both at work and in general) than did the never-exposed, although their symptom reporting was somewhat less than that of the currently exposed. Symptoms with the greatest differences between past-exposed or currently exposed and never-exposed

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were lightheadedness, tiredness, irritability, and lack of coordination. There were no significant differences in NES test results between the past-exposed and the never-exposed. The functional significance of the study-specific measures of NB dysfunction was determined in a novel way; there are no established normative data on clinical relevance of the NES test battery. Performance on each of nine representative NB test measures was categorized as an "outlier" or not on the basis of dichotomization at the worst fifth percentile of scores in the entire study sample (after adjustment for age, education level, alcohol use, and verbal ability). The number of outliers was summed to create a total outlier score. About 15% of subjects were found to have total outlier scores of 2 or more (maximum possible, 9); this score was selected after the fact for dichotomization of the outlier score. Formerly exposed subjects had a distribution of outlier scores that was nearly identical with that of those who had never worked as painters. Thus, the study found no evidence of cognitive impairment persisting after the end of exposure.

Finally, Daniell and co-workers (1999), in a separate study, focused exclusively on retired workers with prior chronic solvent exposure. The study is distinguished by its sole focus on prior occupational exposure, its array of outcome measures, and its method of assessing the clinical significance of the NB effects. The investigators examined NB effects in two formerly exposed groups: 67 retired painters and 22 retired aerospace manufacturing painters and fuel-cell sealers. Each group was compared with 126 retired carpenters who had no previous substantial occupational solvent exposure. Participation rates were relatively low (25–31% of those approached) but did not differ substantially among the three groups. The painters and aerospace workers had worked in solvent-exposed jobs for at least 9 years (mean, over 30 years), and all subjects had been retired for at least 6 months (mean, 6 years). The outcome measures were the results of 21 NB tests, symptom questionnaires (including the Beck depression inventory), psychiatric diagnoses, and outlier scores (which provide an indication of functional significance).

Solvent exposure among the painters was weighted by duration of exposure and intensity derived from a detailed interview. The painters and the aerospace workers had similar cumulative exposure to solvents. Age, alcohol use, educational achievement, race, and vocabulary score were included in the multivariate analysis with exposure level. The 21 NB tests covered six domains, with at least three tests for each domain: language, reasoning, attention, memory, visuomotor speed, and motor. The results reported here emphasize overall scores for a domain rather than individual NB-test results. The painters performed significantly worse than carpenters on overall motor score (three NB test results—finger tapping, grooved pegboard, and simple-reaction time—combined). The painters also showed a dose–response relationship for cumulative exposure and performance on a single test, the block design. Overall motor score was marginally significant ($p = 0.06$) for cumulative exposure. Aerospace workers with medium or high cumulative exposures ($n = 8$) performed significantly worse on overall scores for visuomotor speed—trails A, digit–symbol from WAIS-R, and d2 test (accuracy score)—and motor function. Aerospace workers with low cumulative exposure did not differ from the carpenters on NB tests. With regard to symptoms and diagnoses, the painters were more than twice as likely as carpenters to report three or more symptoms (OR = 2.6, 95% CI = 1.3–5.1), including fatigue, memory problems, and difficulty concentrating. Painters also had a significantly higher score on the Beck depression inventory, which indicates that they had more depression symptoms, but their overall scores were below the range for a diagnosis of depression. Depression scores

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were unrelated to alcohol use. Painters were more likely to have clinically diagnosable alcohol dependence or overuse but had no more evidence of NB effects than did aerospace workers. The aerospace workers were no more likely than the carpenters to have higher symptom reporting, except for getting a "high" from chemicals. An outlier test score provided an indication of the functional significance of the NB effects. The outlier score used 17 representative NB-test measures and a threshold based on the worst 10th percentile of adjusted test performance among the carpenters. Most subjects, including 77% of the carpenters, had no more than two outliers (maximum possible, 17). The painters were more likely than the carpenters to have a total outlier score of at least 3 (OR = 3.1, 95% CI = 1.5–6.2). A higher risk of having an outlier was also seen among the aerospace workers with medium or high cumulative solvent exposure (OR = 5.6, 95% CI = 1.0–3.8). The painters, in contrast, showed no differential in risk associated with cumulative exposure. The study noted that 85% of the test outliers were 1 or more standard-deviation units below the outlier threshold; this indicates that the outliers at least represented a substantial departure from average test performance. Neither this study nor the 1993 study (Daniell et al., 1993) examined the possible relationship between outlier score and reported symptoms. The authors interpreted their findings, including the dose-dependent effects, as indicating residual CNS dysfunction after the cessation of long-term exposure.

One study evaluated by the committee (Rasmussen and Sabroe, 1986) was difficult to interpret because its analysis excluded about one-fourth of the subjects without explanation. Finally, two studies of Dutch painters by Hooisma and colleagues (1993, 1994) included workers (retired painters) with an exposure-free interval, but the authors did not perform a separate analysis comparing them with currently exposed workers or to a nonexposed group.

Summary and Conclusion

Using strict inclusion criteria, the committee evaluated several studies of chronic occupational solvent exposure and NB effects. The studies, of workers with years-long or career-long exposure, were selected by the committee on the basis of an exposure-free interval to ensure that the effects were long-term rather than short-term. Most studies found a variety of decrements in NB-test performance and greater symptom reporting. The sole study with exclusive focus on formerly exposed workers found poorer performance on motor and visuomotor types of NB tests (Daniell et al., 1999). Many of the abnormal findings displayed a dose–response relationship. Both solvent-exposed groups were more likely to have significantly greater outlier scores for NB performance, an indication of clinical significance. The affected domains and the dose-response relationship were similar to those found by Mikkelsen and colleagues (1988). That well-designed study found a dose-dependent visuomotor deficit and a visuospatial deficit. Daniell and co-workers (1999) also found greater symptom reporting in one exposed group, especially for fatigue, difficulty in concentrating, and depression. Supportive evidence came from a well-designed study by Stollery (1996). This study tracked highly exposed female workers for 3 years after a solvent accident. Before the accident, the workers had chronic exposures. At the 3-year mark, the workers involved in the accident had NB-performance decrements on syntactic and semantic reasoning in comparison with a group that had similar chronic exposure but no exposure during the accident. Finally, the occupational findings reported in this section are consistent with a population-based study of Gulf War veterans (Kang et al., 2002). That study found a

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cluster of neurologic symptoms related to solvent exposure, although there was no dose–response analysis and no NB testing.

The types of symptoms reported after chronic exposure varied to some degree, as might be expected given the inherently subjective nature of NB symptoms. The most commonly reported symptoms are fatigue, headaches, difficulty in concentrating, in coordination, and mood symptoms. The study of Gulf War veterans found a cluster of symptoms related to dizziness and balance (Kang et al., 2002).

The clinical significance of the NB effects reported here is supported by the study of Daniell and colleagues (1999). It is also consistent with the body of case–control and retrospective cohort studies of chronic occupational solvent exposure, which found an excess of assorted psychiatric or neurologic diagnoses.[12] The committee also evaluated that body of evidence. Most of the studies reported some degree of excess risk for clinically significant morbidity associated with a variety of neuropsychiatric diagnoses. Although the body of studies cannot be used to support a single diagnostic entity, because of variable and vague classifications, it is consistent in supporting the overall clinical significance of the NB effects described and evaluated in this section.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between past chronic exposure to at least one of the solvents under review, in occupational studies, and neurobehavioral effects. The most consistently affected neurobehavioral domains are visuomotor and motor functioning. The most consistently reported symptoms in occupational solvent studies are fatigue, headache, and difficulty in concentrating, in coordination and mood symptoms.

INSECTICIDES AND NEUROLOGIC DISEASES

This section examines the relationship between exposure to insecticides and neurologic diseases: Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. Studying the relationship between exposure and neurologic diseases poses methodologic challenges, including diagnostic uncertainty, presumed long latency, and concern about the reliability of self-reporting of past exposure, especially in patients with cognitive impairment or difficulty in communicating. The committee considered only studies that specifically examined exposure to insecticides, as opposed to the broader category of pesticides, because the latter includes herbicides and fungicides. Most studies were concerned with occupational exposure rather than with residential or leisure exposure. The committee found no case–control or cohort studies that specifically examined the relationship between insecticide exposure and multiple sclerosis.

[12]Axelson et al. (1976), Brackbill et al. (1990), Cherry et al. (1992), Labreche et al. (1992), Lindstrom et al. (1984), Mikkelsen (1980), Nelson et al. (1994), Olsen and Sabroe (1980), Palmer et al. (1998), Rasmussen et al. (1985), Riise and Moen (1990), Riise et al. (1995), van Vliet et al. (1989, 1990).

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Parkinson's Disease and Insecticide Exposure: Background and Epidemiologic Studies

Parkinson's disease (PD) is a chronic, progressive neurologic disease that affects about 40,0000–60,0000 people in the United States. The disease generally afflicts people over 45 years old. As the population ages, the prevalence of PD in the United States is projected to increase to 1.3 million by the year 2040 (Muir and Zegarac, 2001).

PD is characterized by clinical manifestations that include tremor, bradykinesia, rigidity, and postural instability. When those manifestations occur without a progressive course or other manifestations, such as dementia or ataxia, they are more broadly denoted as parkinsonism. Some neurotoxicants can cause a Parkinsonian-like syndrome, such as manganese, carbon monoxide, and the contaminant in synthetic heroin, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Manganese damages a different part of the CNS than does MPTP. Furthermore, MPTP neurotoxicity is called Parkinsonian-like, rather than Parkinson's Disease in most of the literature.

The discovery of MPTP-induced parkinsonism in 1982 stimulated a new line of investigation into pesticides in the etiology of PD. Driving that line of investigation is the structural similarity between the biologically active form of MPTP, 1-methyl-4-phenylpyridinium ion, MPP^+ [13] and the herbicide paraquat, widely used for the control of weeds.

The etiology of PD is not well understood. The body of epidemiologic evidence relating pesticides to PD comes from case–control and ecologic studies. In a recent ecologic study, Ritz and Yu (2000) showed a 19–47% higher mortality from PD than from ischemic heart disease in California counties where pesticide exposure was reported. Genetic factors are also thought to play a role in the onset of PD, but their contribution appears to decrease after the age of 50 years (Tanner et al., 1999). Genetic factors may contribute to susceptibility by influencing the toxic effect of pesticides on the CNS. A complex, multifactorial etiology of PD is suggested by Hubble and colleagues (1993), who found that the combination of pesticide exposure, family history of neurologic disorders (including PD, Alzheimer's disease, tremor, or palsy), and depression results in an extremely high probability of developing PD. In the absence of those combined factors, the probability of developing PD was significantly lower.

Many epidemiologic studies have attempted to ascertain environmental risk factors for the development of PD. Respondents in epidemiologic studies often have difficulty in remembering specific agricultural exposures, so many investigators have simply asked generic questions about exposure to "pesticides." Much of the literature deals with pesticide exposures that may include exposure to herbicides as well as to the insecticides of interest to the committee. In its evaluation, therefore, to ensure that the study groups were as homogeneous as possible, the committee included only studies of insecticides, rather than of the umbrella category of pesticides; studies with case–control or cohort designs; and studies

[13]Since its discovery, much insight has been gained into the mechanism of MPTP toxicity. Understanding this mechanism may shed light on a possible relationship between other exogenous exposures and parkinsonism. MPTP enters astrocytes, where it is converted to the active form, MPP+, by monoamine oxidase B. MPP^+ enters the dopaminergic neurons of the nigrostriatal system through the reuptake mechanism. In the neuron, MPP^+ blocks mitochondrial respiration at the complex I ubiquinone binding site, a blockade that results in cell death (Cleeter et al., 1992). Loss of neurons in the nigrostriatal system is the primary pathologic finding in PD.

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of PD rather than of the more general diagnosis of parkinsonism.[14] The committee excluded studies that listed "farming" as an occupation if they did not specify the nature of the exposure.

Numerous case–control studies addressed the relationship between pesticide exposure and PD. Those studies evaluated patients for exposure via interview or questionnaire and then compared the prevalence of exposure among cases with that among a group of nondiseased controls. Of the case–control studies, the committee identified six as meeting its inclusion criteria. The six studies (Table 7.8) typically obtained information about past exposures from cases and controls and then developed a job–exposure matrix. Because exposure data rely for the most part on self-reports, there is the possibility of misclassification bias, a common limitation of case–control studies. In addition, the fact that people with PD may be more motivated to remember exposures that they perceive as being responsible for their disease can result in recall bias.

Butterfield and colleagues (1993) studied 63 patients from Oregon or Washington with early onset PD and 68 controls diagnosed with rheumatoid arthritis. They found PD to be positively associated with insecticide exposure over 10 times per year (adjusted OR = 5.75, $p = 0.001$). The study used good diagnostic criteria, but exposure was defined as having occurred at any time before diagnosis (as long as it was at least 10 times per year). That might have led to inclusion of exposure that occurred after the onset of PD, which would bias the estimate of effect. Another limitation was that only 69% of eligible cases and only 41% of controls participated. If a decision to participate was related in some way to the exposure, the estimate of effect could be biased. Finally, no information on dose–response relations was reported, and this limits the interpretation of the results.

The work of Gorell and colleagues (1998) was judged by the committee as the most methodologically rigorous study of the relationship between insecticides and PD. This study of a Detroit primary-care population in a single health system found a strong positive association between occupational insecticide exposure and PD (adjusted OR = 3.55, 95% CI = 1.75–7.18). The subset of people with occupational exposures of over 10 years had higher odds ratios than the subset with less than 10 years. Advantages of the study were explicit diagnostic criteria and inclusion of subjects who had at least one visit to a primary-care specialist within 5 years before enrollment (this ensures matching of cases and controls with respect to access to care). Two other advantages were its exclusion of cases and controls with a low score on the Mini-Mental Status Examination to reduce inclusion of cognitively impaired study subjects and its exclusion of controls who had symptoms that might be early signs of PD. One limitation was inclusion of all exposures until the time of diagnosis, which would include post-onset exposure. In addition, the risk-factor questionnaire focused on occupational exposure, which could have alerted subjects to the objective of the study. The authors were unable to assess the independent effects of herbicides and insecticides, because samples were small.

[14]The inclusion of parkinsonism studies in the evaluation might have attenuated any possible associations between insecticides and Parkinson's disease. The committee separately evaluated two studies of insecticide exposure and parkinsonism. Both were case–control studies, and both found no association in subgroups with insecticide exposure (Engel et al., 2001, Herishanu et al., 1998).

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TABLE 7.8 Case–Control Studies of Parkinson's Disease and Insecticide Exposure

Reference, Country	Cases	Controls	Exposure Determination	Insecticide Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI or *p*)	Comments
Butterfield et al., 1993 US	63 patients with early-onset PD; diagnosed before age 51 years; referred by physicians or other patients; Mean duration of disease 9 years from diagnosis; 69% response	68 persons diagnosed with rheumatoid arthritis; frequency-matched for sex, birth year, year of diagnosis; 41% response	Self-report questionnaire; Reconstruction of employment, exposure history	Ever lived in fumigated house Ever lived within ¼ mile of agricultural spraying Insecticide exposure over 10 times per year	3.29 ($p = 0.068$) 1.99 ($p = 0.106$) 4.04 ($p = 0.002$)	5.25 ($p = 0.045$) 1.99 ($p = 0.099$) 5.75 ($p = 0.001$) 7.24 (2.29–22.92) 4.30 (1.35–13.67)	Adjusted for age, age at diagnosis, race, sex, educational level, family history of PD; also adjusted for smoking; also adjusted for eating seeds and nuts, rural residency, and past residence in fumigated house; Participation very low in cases, controls
Gorell et al., 1998 US	144 PD patients receiving primary medical care from single health system; diagnostic criteria used; MMSE result under 24 excluded; Mean duration of disease 2.4 years from diagnosis	464 controls frequency-matched for age, race, sex; controls reporting symptoms of potentially undiagnosed PD excluded; MMSE result under 24 excluded	Questionnaire administered face to face by trained interviewers; Lifetime-exposure measure calculated from responses; Exposure up to time of diagnosis	Residential insecticide spraying Gardening insecticide exposure Farm residence insecticide exposure Occupational insecticide exposure: Overall <10 years >10 years Adjusted for farming	1.02 (0.62–1.65) 0.88 (0.58–1.36) 1.4 (0.76–2.59) 3.11 (1.56–6.15)	1.03 (0.63–1.7) 0.90 (0.58–1.38) 1.28 (0.69–2.4) 3.55 (1.75–7.18) 2.39 (0.89–6.4) 5.80 (1.99–16.97) 3.15 (1.54–6.49)	Adjusted for race, age, sex, smoking status; Questionnaire distinguished insecticide from herbicide, fungicide exposures; Only four patients, 11 controls could identify one or more subclasses of insecticides they were exposed to

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Reference, Country	Cases	Controls	Exposure Determination	Insecticide Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI or *p*)	Comments
Hertzman et al., 1994 Canada	127 PD patients identified by their physicians, examined by neurologist to confirm diagnosis; Mean duration of disease 7 years from onset	121 patients with cardiac disease identified by their physicians (79% participation rate); 124 randomly selected from list of voters (61% participation rate)	Trained interviewers blinded to study hypothesis; Exposure before date of onset	Ever exposed to insecticides: men vs cardiac controls vs voter controls women vs cardiac controls vs voter controls	 0.62 (0.28–1.38) 0.33 (0.12–0.90) 0.65 (0.27–1.57) 0.41 (0.19–0.88)		Pesticides associated with fruit-tree industry; cue cards with details on 79 specific pesticides presented to respondents; Results also presented for OPs, OCs, carbamates (none significant); Protective findings; inconsistent with all other studies
Seidler et al., 1996 Germany	380 PD patients from nine neurology clinics staffed by neurologists with special interest in PD; Patients 65 years old or less at diagnosis; Mean duration of disease: 5.6 years from onset, 3.7 years from diagnosis	379 control subjects matched by age, sex; recruited from same neighborhood with random route method; 376 controls recruited from elsewhere in same region	Experienced interviewers blinded to hypothesis; Complete residential history with detailed pesticide exposure, including names of agents where possible; Job-exposure matrix to assess occupational exposures	Insecticide Use: vs neighborhood controls: never 1–40 dose–years 41–80 dose–years >80 dose–years vs regional controls: never 40 dose–years 41–80 dose–years 80 dose–years Organochlorines ever: vs neighborhood controls vs regional controls Alkylated phosphates and carbamates ever: vs neighborhood controls vs regional controls	 1.0 1.4 (0.9–2.1) 1.5 (0.9–2.5) 1.6 (0.7–3.4) *p*- trend = 0.12 1.0 1.8 (1.1–2.7) 2.5 (1.4–4.5) 2.1 (0.9–4.8) *p*- trend = 0.001 1.6 (0.4–6.2) 5.8 (1.1–30.4) 1.8 (0.9–3.3) 2.5 (1.3–4.6)	Adjusted for smoking and education; “Dose–years” calculated by assigning a 1–3 frequency-of-usage weight to each year of exposure; No mention of results of using job-exposure matrix

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Reference, Country	Cases	Controls	Exposure Determination	Insecticide Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI or *p*)	Comments
Semchuk et al., 1992 Canada	130 patients selected from population-based register of neurologist-confirmed PD cases; Demented excluded (on basis of clinical assessment); Mean duration of disease: 7.8 years from diagnosis, 10 years from onset	260 age- and sex-matched community controls selected by random- digit dialing	Lifetime occupational history with details about dates of chemical exposure on each job, exposures after age 15, jobs held over 1 month; Interviewers, subjects blinded to study hypotheses	Occupational insecticide use Occupational use of insecticides between ages 46–55 years	2.05 (1.03–4.07) 3.50 (1.03–11.96)	1.48 (0.68–3.24)	Adjustment for herbicide use; ORs consistently higher for herbicide than insecticide exposure; only herbicide use consistently associated in linear-regression models; No association with duration of pesticide exposure
Stern et al., 1991 US	69 patients with PD; onset before age of 40 years; identified from neurology departments at two university hospitals; 80 with PD onset after age 60 years, randomly chosen from patients at one institution	149 age- and sex-matched, randomly selected from nonfamily acquaintances; nominated by cases	Structured interview, including lifetime residential histories; Apparently, no data on occupational exposures collected	Exposure to insecticides in home, yard, garden, neighborhood by members of household or professionals ever Among young subset, exposure to any insecticide Among older subset, exposure to any insecticide	0.7 (0.3–1.4) 0.6 (0.2–1.7) 0.8 (0.3–2.1)	0.5 (0.2–1.1)	Adjustment for smoking, prior head injury, previous rural residence; Very broad exposure measure; 89% of respondents reported insecticide exposure; Choice of controls based on nomination by cases may have resulted in too-similar control group

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Hertzman and colleagues (1994) studied 127 Canadian PD patients identified by their physicians and compared them with cardiac-disease controls and with controls selected from electoral lists. The study made the most aggressive attempt to assess exposure to specific agents. It was conducted in a region with a high prevalence of orchard chemicals and an agricultural office, which provided records of specific pesticides and dates of marketing. From that information, the investigators created cue cards with full descriptions of 79 agricultural chemicals to aid subjects' memories. Analysis was performed for pesticides in general, insecticides in general, and specific insecticide classes. The study found a positive association between pesticide exposure and PD. But the opposite—a protective effect—was found specifically for insecticide exposure: the confidence intervals for PD were entirely below 1 for both men and women with past insecticide exposure compared with electoral-list controls. No positive associations were found for exposures to OPs, organochlorines, or carbamates. The study was limited by differential ascertainment between cases and controls. One control group was restricted to voters, but cases were not restricted in this manner. That might be important if cases included migrant workers or other noncitizens working in orchards; such inclusions would tend to increase the likelihood of exposure in the cases. The finding of a protective effect of insecticides is inconsistent with findings from other studies discussed in this part of the chapter.

Seidler and colleagues (1996) studied 380 PD patients from nine neurology clinics in Germany. The authors did not find positive associations between insecticide exposure and PD when they used neighborhood controls, but they did when they used regional controls (although not at the highest dose). They also found a positive association with exposure to organochlorine and alkylated phosphates or carbamates. The study's advantages were large size, good diagnostic criteria, blinding of interviewers to the study hypothesis, and categorization of pesticide exposures by a toxicologist. Its limitations were recruitment of cases from clinics with a "special interest in PD," which might result in inclusion of unusual cases. Regional (but not neighborhood) controls were recruited by random selection from electoral rolls. If there were demographic differences between cases and controls, they may be related to exposure, thereby increasing the likelihood of observing a positive association. Another problem was that cases were asked about exposure that occurred at any time before diagnosis, but controls were asked about exposure only one year prior to interview. Thus, cases were asked to remember exposure over a longer period, which might have attenuated effects. Another limitation was that the results from analyzing exposure with a job-exposure matrix were not reported.

Semchuk and colleagues (1992) studied Canadian patients from a population-based registry and community controls. They found a positive association with insecticides, but the association disappeared after adjustment for occupational herbicides. The study had the advantages of being population-based, of excluding people with dementia, and of restricting analysis to exposures with long latency. One limitation was having the primary author review occupational history, which introduced the possibility of bias. Another was the long disease duration in cases (mean duration from onset to evaluation, 7.8 years), which introduced the problems associated with patients' recall of predisease risk factors and the potential for survival bias.

Stern and colleagues (1991) studied patients with early-onset and late-onset PD. They found no positive association with insecticide use in the home, yard, or garden, but

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their findings were limited by lack of occupational-exposure information and by the separation of exposure into "any exposure" and "none."

Summary and Conclusion

The six studies reviewed here offer conflicting results about the relationship between insecticides and PD. Three of the studies found no association (Seidler et al., 1996; Semchuk et al., 1992; Stern et al., 1991), one found a protective effect (Hertzman et al., 1994), and two found a positive association between insecticides and PD. Of the two positive studies, Butterfield and colleagues (1993) reported the highest odds ratios but was limited by low participation rates, which were considerably different between cases and controls. The best-designed study, Gorell and colleagues (1998), was hampered by its consideration of all exposures until the time of diagnosis, which could have included post-onset exposure.

The studies varied widely in reliability of their estimates of exposure. Investigators in some of the studies took more-detailed residential or occupational exposure histories and attempted to determine whether higher exposure led to increased risk of PD. Results, again, were mixed: two studies showed higher odds ratios at higher exposures (Butterfield et al., 1993; Gorell et al., 1998), and two found no association with duration of exposure to insecticides (Hertzman et al., 1994; Semchuk et al., 1992). Overall, because of the potential for bias, including confounding, these studies do not provide good evidence of an association between insecticide exposure and PD.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and Parkinson's disease.

Amyotrophic Lateral Sclerosis and Insecticide Exposure: Background and Epidemiologic Studies

Amyotrophic lateral sclerosis (ALS) is a rapidly fatal neurologic disorder characterized by progressive muscle weakness, muscle atrophy, and fasciculations. The disease is associated with degeneration of motor neurons in the spinal cord. Because ALS affects only motor neurons, the disease does not impair a person's mind, personality, intelligence, or memory. Nor does it affect a person's senses. About 20,000 people living in the United States are afflicted with ALS, and an estimated 5000 people are diagnosed each year. ALS is most commonly diagnosed in people 40–60 years old, but younger people can also develop it. Men are affected slightly more often than women. Of all ALS cases, 90–95% are sporadic with no known risk factors and 5–10% are inherited. Although the etiology of ALS is unknown, some epidemiologic studies have suggested a relationship between lead exposure and ALS, because toxic lead concentrations can produce symptoms similar to those of ALS (Kamel et al., 2002). In North America, investigators generally use the term *ALS* in reference to three motor neuron diseases: ALS (the most common), progressive bulbar palsy (PBP), and progressive muscular atrophy (PMA). In Europe, investigators refer to ALS and classify the two other diagnoses as subtypes of the more generic term *motor neuron disease* (MND). PBP has the most rapidly fatal course, and PMA the most benign (Verma and Bradley, 2001). If the three diseases have different etiologies, differing case mixes within studies would render comparisons across studies difficult. To

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date, there is no evidence that the etiologies differ, although no studies have addressed this specific issue.

The committee identified five case–control studies that examined the association between ALS and exposure to agricultural chemicals. Four did not specifically address exposure to insecticides but used broader categories, such as "pesticides" or "agricultural chemicals," in their characterization of exposure; and they did not report positive associations (Chancellor et al., 1993; Deapen and Henderson, 1986; Granieri et al., 1981; Savettieri et al., 1991).

The fifth study did specifically address exposures to insecticides. McGuire and colleagues (1997) identified all newly diagnosed ALS patients in a three-county region in western Washington State using a surveillance system. Two controls were matched to each case with one of two techniques: random-digit dialing for cases under 65 years old and Medicare eligibility lists for older cases. The participants were 174 patients with ALS and 348 controls. Exposure information was obtained with a detailed interview that gathered information on all jobs held for at least a year since the age of 15 years. Job information included detailed descriptions of tasks performed and hours worked per week. Subjects also reported on exposures to 28 specific chemical agents, use of protective equipment, and exposure to any accident, spill, or explosion. Information about home activities and hobbies was also gathered. A panel of four industrial hygienists, blinded to the patient's disease status and self-reported assessment of exposure, rated workplace exposure. ALS was found to be moderately associated with the hygienist panel's assessment of insecticide exposure (OR = 2.1, 95% CI = 1.1–4.1) but not with the patients' self-reports (OR = 1.0, 95% CI = 0.5–1.8). A dose–response gradient with insecticide exposure was found only for men. In a conditional logistic-regression analysis adjusting for age and education and using the hygienists' assessments of exposure, the OR for low exposure was 2.0 (95% CI = 0.5–7.7), and it rose to 2.8 with high exposure (95% CI = 1.1–6.8). The study, however, had several limitations. Cases were less educated than controls, possibly creating a disparity that may have led to a selection bias in the direction of overestimating an effect. There was a higher refusal rate in controls than in cases, which might have resulted in a selection bias of unknown direction. The authors themselves comment that their findings are exploratory.

None of the reports about Gulf War veterans published in peer-reviewed journals specifically addressed ALS. However, a large government-funded epidemiologic study provides preliminary evidence that veterans who served in the Gulf War are nearly twice as likely as their nondeployed counterparts to develop ALS (Feussner, 2002). The committee was unable to obtain preliminary copies of the report for review and therefore could not evaluate its findings in reaching conclusions about insecticide exposure and ALS.

Summary and Conclusion

Only one peer-reviewed study (McGuire et al., 1997) expressly examined the relationship between insecticides and ALS. That study provided evidence of a relationship, but the possibility of selection bias resulting in an overestimation of effect cannot be excluded. There were no other studies with which to compare results.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and Amyotrophic Lateral Sclerosis.

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Alzheimer's Disease and Insecticide Exposure: Background and Epidemiologic Studies

Alzheimer's disease (AD) is a neurodegenerative disease marked by progressive impairment in cognition and memory. It is the most common form of dementia in older people, with a prevalence of about 5% over the age of 65 years. AD is more common in women than in men. A variety of risk factors have been studied, but only age, family history, head trauma, fewer years of formal education, and presence of the apolipoprotein 4 allele show consistent results (CSHA, 1994; Hendrie, 1998). Nonsteroidal anti-inflammatory drugs and estrogen have been reported to be protective in a few studies (Paganini-Hill and Henderson, 1994; Wolfson et al., 2002). There is no evidence of a geographic gradient in incidence or prevalence. Because of the cognitive deficit in those suffering from AD, epidemiologic studies require the use of proxy respondents to obtain information on past exposure and lifestyle factors (Weiss et al., 1996).

In reviewing the evidence of insecticide exposure as a risk factor for AD, it is worth noting that one particular OP insecticide, metrifonate, has been investigated in the clinical setting as a potential treatment for AD. Because its mechanism of action involves the depletion of acetylcholine (Ormrod and Spencer, 2000), metrifonate was proposed to raise acetylcholine through its action as an irreversible acetylcholinesterase inhibitor with relatively low potency (Spencer et al., 2000). Metrifonate (under the insecticide name trichlorfon) had been tested in clinical trials, but the manufacturer withdrew its application to the Food and Drug Administration in 2000, when the trials uncovered a small number of cases of respiratory paralysis. Metrifonate has been used outside the United States since the 1960s by the World Health Organization to treat schistosomiasis.

The committee identified two studies that focused specifically on the relationship between insecticides and AD. Several other epidemiologic studies examined the relationship between the disease and pesticides but not insecticides (CSHA, 1994; French et al., 1985). Two other studies used occupational classes (such as farming) as proxies for exposure and so were too general for the committee's consideration (Amaducci et al., 1986; Schulte et al., 1996).

Gauthier and colleagues (2001) studied environmental risk factors in a randomly selected group of 1924 older residents of Quebec, Canada. Of this group, 68 cases were compared with nondemented controls through structured questionnaires of subjects and proxy respondents. The investigators also used residential histories and agriculture census histories for herbicide and insecticide spraying (1970–1991). The study found no association between past insecticide (or herbicide) exposure and AD.

Gun and colleagues (1997) examined past occupational risk factors in 170 patients with AD and 170 medical-practice-based controls (matched for age and sex). Occupational exposures included "organophosphates" and "hydrocarbon solvents." Occupational histories were gathered from informants (proxies) for both patients and controls, and exposure was assessed by a panel of occupational hygienists (blinded to case or control status). The study found no association between OP insecticides and AD.

Summary and Conclusion

The two case–control studies reviewed found no associations between insecticides and Alzheimer's disease (Gauthier et al., 2001; Gun et al., 1997). Other studies did not

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specifically examine insecticide exposure but focused on the broader category of "pesticides." The occupational studies reviewed used occupations as surrogates for exposure, but the committee was unable to determine whether exposure relevant to the Gulf War had occurred.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and Alzheimer's disease.

SOLVENTS AND NEUROLOGIC DISEASES

This section addresses the association between exposure to solvents and four neurologic diseases: Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Alzheimer's disease. Those diseases have distinct sex and age distributions and pose numerous challenges to epidemiologic research, such as diagnostic uncertainty, presumed long latency, and concern about the reliability of self-reported exposure information from patients with cognitive impairment or inability to communicate. The committee evaluated the body of evidence on solvent exposure and neurologic disorders almost exclusively from case–control studies. The design of the studies is inherently subject to a number of potential biases, some of which cannot be avoided. Those limitations are described in the context of each study that the committee evaluated.

Parkinson's Disease and Solvent Exposure: Epidemiologic Studies

PD is described earlier in this chapter. The committee evaluated studies only with PD as the outcome measure rather than the more generic diagnosis of parkinsonism, as explained earlier. Only two studies were found to be sufficiently rigorous in design to be useful in providing evidence on the relationship between solvent exposure and PD (Hertzman et al., 1994; Seidler et al., 1996). One of them (Hertzman et al., 1994) focused on pesticides and presented little pertaining to solvent exposure. Both were case–control studies that used prevalent cases (Table 7.9).

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TABLE 7.9 Parkinson's Disease and Solvent Exposure

Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR (95% CI)	Adjusted OR (95% CI)	Comments
Hertzman et al., 1994 Canada	127 PD patients identified by their physicians, examined by neurologist to confirm diagnosis; Mean duration of disease 7 years from onset	121 patients with cardiac disease identified by their physicians; 124 randomly selected from list of voters	Trained interviewers blinded to study hypothesis; Exposure before date of onset	Ever exposed to solvents in occupation: men: vs cardiac controls vs voter controls women: vs cardiac controls vs voter controls	 1.80 (0.91–3.58) 2.16 (1.07–4.37) 1.34 (0.42–4.25) 1.20 (0.48–3.01)		Electoral list would have to be citizens but no such exclusion for cases; Primary focus on pesticides
Seidler et al., 1996 Germany	380 PD patients from nine neurology clinics staffed by neurologists with special interest in PD; Patients 65 years old or less at time of diagnosis; 71% participation rate; Mean duration of disease: 5.6 years from onset, 3.7 years from diagnosis	379 control subjects matched by age, sex recruited from same neighborhood with random–route method; 376 controls recruited from elsewhere in same region with same methods	Experienced interviewers blinded to hypothesis; Complete residential history with detailed exposure, including names of agents where possible; Job–exposure matrix to assess occupational exposures	Solvents: vs neighborhood controls: never in free time at work vs regional controls: never in free time at work	 	 1.0 2.6 (1.2–5.4) 1.6 (1.1–2.4) 1.0 3.4 (1.5–7.5) 1.8 (1.2–2.7)	Adjusted for smoking and education; No associations found when job–exposure matrix used as measure of exposure

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Hertzman and colleagues (1994) studied 127 Canadian PD patients identified by their physicians and compared them with cardiac-disease controls and healthy controls drawn from electoral rolls. The latter control group was chosen to reduce the impact of potential recall bias. Exposure was ascertained in face-to-face interviews. The main focus of the study was on pesticides, but there was one exposure question about occupational exposure to solvents. Exposure was defined only as ever or never exposed before reported onset of disease. When cases were compared with controls from the electoral rolls, a moderate association between occupational exposure to any solvents before disease onset was found for men (OR = 2.16, 95% CI = 1.07–4.37). No association was found for men in comparison with the cardiac-disease controls or for women in comparison with either control group. The validity of the association—men with PD compared with electoral-list controls—is limited for three reasons. The first is a difference in findings depending on the control group; the association only with the electoral-list controls suggests that the finding is a result of recall bias from underreporting of exposure by this group of controls. The second is the use of the electoral list as the source of the healthy control group. Noncitizens were excluded, and this exclusion was not applied to the case group. If citizenship status is related in some way to the probability of being exposed to solvents, the comparison between cases (including noncitizens) and controls (excluding noncitizens) may be biased. It is difficult, however, to predict the direction of the bias in terms of either underestimating or overestimating the effect of solvents on PD occurrence. The third is that the focus of this study was the relationship between pesticides and PD, not solvents and PD. As a result, the method describing solvent-exposure assessment is only briefly presented, and the analysis is limited.

Seidler and colleagues (1996) studied 380 PD patients from nine neurology clinics in Germany. The UK PD Society Brain Bank clinical diagnostic criteria were used to screen subjects for eligibility. Potential cases with dementia or secondary parkinsonian syndromes were excluded. Cases were compared with two control groups that were population-based and were recruited with the random-route procedure in which the interviewer contacts every second household, starting with the patients. In addition to the natural matching on residence, the controls were matched on sex and age ±3 years. The investigators elicited information on exposure to "solvents"–never, in free time, or at work. Controls were asked to report exposure at any time at least a year before interview, but cases reported exposure at any time before diagnosis. Because the cases had average illness duration of 3.7 years, that discrepancy meant that controls did not have to remember as far back. A detailed occupational history was also collected from each study subject, from which a panel of experts constructed a job–exposure matrix. Conditional logistic regression was used to analyze results, and smoking and education status were included as covariates in the model.

Seidler and colleagues (1996) reported positive associations regardless of whether the self-reported exposure was to solvents at work or in free time. Contrary to expectations, free-time exposure resulted in higher odds ratios than did work exposure. When the exposure assessment using the job–exposure matrix was used, no association was found. It is generally accepted that although a job–exposure matrix is itself based on information obtained from self-reports, it provides a more accurate measure of occupational exposure. The discrepancy in findings between the two types of exposure variables (self-report vs job–exposure matrix) suggests recall bias through possible underreporting of exposure in

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controls relative to cases. Other study limitations are discussed in the section above on insecticides and PD.

Summary and Conclusion

Two studies found an association between past exposure to solvents and PD, but both studies were likely to have been subject to recall bias. It should be noted that little attention has been focused on solvent exposure as a risk factor for the occurrence of PD.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and Parkinson's disease.

Amyotrophic Lateral Sclerosis and Solvent Exposure: Epidemiologic Studies

This section addresses the association between solvent exposure and ALS. Four case–control studies (Table 7.10) were evaluated by the committee (Chio et al., 1991; Gunnarsson et al., 1992; McGuire et al., 1997; Strickland et al., 1996). One was a pilot study of only 25 cases and 50 controls (Strickland et al., 1996). Mortality studies using only death certificates (Hawkes et al., 1989; Neilson et al., 1994) and a study of the occupational distribution of ALS cases in Greece (Kalfakis et al., 1991) were excluded because the committee could not ascertain the nature of the exposure in those studies.

Gunnarsson and colleagues (1992) studied cases and controls in a nine-county region of Sweden. Cases, which were recruited from all departments of neurology and internal medicine, had any one of the three diagnoses subsumed under "motor neuron disease." A self-administered questionnaire was mailed to study subjects to gather information on current and past occupational, physical, and chemical exposure. Exposure of controls occurring within 5 years before the date of completion of the questionnaire was excluded, as were case exposures occurring within 1 year of symptom onset. Additional potential confounders were contact with animals, physical trauma, use of aluminum utensils, and lack of exercise. Exposure to solvents was reported to be rare in women. For men, none of the occupational solvent-exposure categories (including the umbrella category of "any solvent" exposure) yielded positive associations. A strong association was found for the combination of male sex, any occupational exposure to solvents, and heritability (a family history of neurodegenerative disease or thyroid disease) (OR = 15.6, 95% CI = 2.8–87.0). Because that combination occurred in seven cases and three controls, the result, if valid, is unlikely to be responsible for a large proportion of cases in the population.

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TABLE 7.10 Amyotrophic Lateral Sclerosis (Motor Neuron Disease) and Solvents

Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI)	Comments
Gunnarsson et al., 1992 Sweden	112 cases of MND, age 45–79 years; from departments of neurology and internal medicine in nine counties; ALS: lower motor neuron symptoms in at least two regions; symptoms of upper motor neuron involvement within 3 years after onset; PBP: bulbar paresis as dominating symptom but no evidence of upper neuron involvement; PMA: only lower motor neuron involvement during first 3 years; Mean duration of MND 5 years; Prevalent cases	496 controls randomly selected from national population registry	Excluded exposure occurring less than 5 years before 1990; for cases, considered only exposure in last year before onset of MND; Self-administered questionnaire on current and past jobs; Also asked physical and chemical exposure, other factors, including diet, family history; Most solvents were aromatic hydrocarbons, mixed volatile hydrocarbons, petroleum	Men: any occupational solvent (three diagnoses); Combination of male with MND, any solvent exposure, heritability (family history of AD, PD, ALS, thyroid disease); Both sexes combined: any occupational solvent, PMA alone with no trauma	 2.5 (1.0–6.5)	1.3 (0.7–2.5) 15.6 (2.8–87.0)	Exposure to solvents might be confounder with regard to physical trauma

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Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI)	Comments
Strickland et al., 1996 US	25 cases from University of Minnesota ALS clinic; cases selected from "active" clinic; patients living in area; excluded if physical incapacity in mobility or communication; Time since diagnosis 1 month–7 years (mean, 118 weeks); Prevalent cases	50 controls from two sources: 25 community controls from random-digit dialing, matched on age ± 5 years and sex; 25 clinic controls with other neuromuscular diseases, matched on clinic enrollment date; mostly patients with myopathies; matched on sex, age ± 5 years, residence; same exclusion for physical incapacity	Mailed set of interview forms to prepare for in-clinic interview; Questions on work history, times, job description Shown cards listing industries, chemicals; "organic solvents" on card	Occupational exposures: paint or pigment manufacture organic solvents paint thinners		1.9 (0.5–7.4) 1.2 (0.4–3.7) 1.2 (0.3–4.6)	

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Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR (95% CI or *p*)	Adjusted OR (95% CI)	Comments
McGuire et al., 1997 US	174 cases of ALS, PBP, PMA[a] in Washington State (1990–1994); Incident cases	348 controls (two for each case); matched on sex, age ± 5 years, in one of two ways: by random-digit dialing if less than 65 years old, Medicare list if over 65 years old	Interviewers, not blinded to case or control status, conducted detailed interview of jobs held from age 15 years to reference date; Panel of four industrial hygienists rated workplace exposure to 28 agents, depending on job history from interview; blinded to disease status, self-reported exposure; Excluded exposure during 10 years before diagnosis	Both sexes combined: self-report, panel assessment Men: self-report, panel assessment Women: self-report, panel assessment Specific solvents: cleaning solvents, degreasers; self-report, panel assessment		1.6 (1.1–2.5) 1.2 (0.8–1.9) 1.1 (0.6–2.1) 1.3 (0.7–2.3) 2.4 (1.3–4.3) 1.1 (0.6–2.2) 1.8 (1.2–2.8) 1.9 (1.1–3.3)	Cases had less formal education; Matching on age, sex, respondent type (self, proxy for cases; matched controls, if case died before interview)
Chio et al., 1991 Italy	512 cases of MND seen at author's hospital 1960–1982; Diagnostic criteria included electromyography; Prevalent cases	512 controls admitted to same hospital for neurologic diagnoses; matched on date of admission, sex, age, province of residence	Occupational history collected from patient's clinical record; occupation, marital status also collected from municipal records	Occupational exposure: house painter	2.8 (1.6–3.9)		No direct reporting of occupation; No information on duration of employment; types of solvents exposed to; Use of hospitalized controls might be problem if it prevented them from working in some occupations

[a] MND = motor neuron disease; ALS = amyotrophic lateral sclerosis; PBP = progressive bulbar palsy; PMA = progressive muscular atrophy.

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Strickland and colleagues (1996), in a pilot study, investigated the occupational history of patients diagnosed with ALS at the University of Minnesota. Cases were compared with two control groups, one obtained through random-digit dialing and the other from the same clinic but having other neuromuscular diseases (as a means of adjusting for the potential problem of recall bias). Investigators mailed a job-history questionnaire to subjects before an exposure interview to permit them and their proxies to prepare. At the interview, participants were shown cards listing industries with possible exposure to organic solvents. The authors noted that the information they collected "antedated the development of ALS symptoms," but no further detail was provided on the timing of exposure. No associations between ALS and occupational history of solvent exposure were found. The small sample in this study is an important limitation but, even so, the point estimate for solvent exposure is small (1.2), and the confidence intervals include values as small as 0.4. In addition, the use of clinic controls with other neuromuscular diseases may have resulted in a biased estimate of the association, particularly if the control diseases share etiologic factors with the cases.

McGuire and colleagues (1997) used a surveillance system to identify all 174 newly diagnosed ALS patients in a three-county region in western Washington State. Two controls were matched to each case with one of two techniques: random-digit dialing for cases under 65 years old and Medicare eligibility lists for older cases. Exposure, as summarized previously in this chapter, was assessed according to self-reported information and by a panel of four industrial hygienists that rated workplace exposure. Self-reports and panel assessments were also used to determine exposure to 28 specific agents, including 13 solvents. The study found different associations depending on the method of exposure assessment. After adjustment for age and education, a positive association was found between any self-reported exposure to solvents in both men and women (OR = 1.6, 95% CI = 1.1–2.5)—a finding due largely to the association in women (OR = 2.4, 95% CI = 1.3–4.3). Both associations disappeared when exposure was assessed by a panel of industrial hygienists. Of the 28 specific agents, investigators found a single positive association between ALS and exposure to "cleaning solvents or degreasers" according to both self-report (OR = 1.8, 95% CI = 1.2–2.8) and panel assessment (OR = 1.9, 95% CI = 1.1–3.3). Stratified by sex, the association remained for women but not for men, and there was no dose–response relationship. No positive associations were found with 12 other solvents, including those relevant to the committee's mandate: "benzene, toluene, or xylene," "paint, varnish, or stain," and "alcohols or ketones." The limitations in interpreting this study include the discrepancies in findings depending on the type of exposure information (more positive associations based on self-reports than on hygienists' assessments). Finally, there was a higher refusal rate in controls than in cases, which might have resulted in a selection bias of unknown direction. The authors themselves comment that their findings are exploratory, not confirmatory.

Chio and colleagues (1991) conducted a case–control study in Italy. Cases were included if they met specific clinical and electromyographic criteria outlined in a prior study (Chio et al., 1987). Controls were recruited from the same hospital as the cases. The controls were matched on age, date of admission, sex, and province of residence. Occupational data were collected from patients' clinical records and municipal records. Taking into account the matching of the controls to the cases, the authors used a McNemar test for paired data. The authors state that they did not adjust for any other variables, because "previous studies did not unequivocally identify any risk factor." Thus, only crude odds ratios are presented.

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Considering specific occupations, the authors report a moderate association for only one occupation relevant to the committee: house painting (OR = 2.8, 95% CI = 1.6–3.9). The results of this study must be considered in light of the absence of direct reporting of occupation and of duration of employment. A further limitation is the use of hospital controls; this might have been problematic if the reason for their hospitalization was in some way associated with the likelihood of exposure —for instance, if controls were suffering from conditions that would prevent them from working in some occupations—and may have resulted in an underestimation of exposure in this group relative to the cases.

Summary and Conclusion

All studies used prevalent cases. Two used only self-reports of exposure to solvents (dichotomized as ever or never) (Gunnarsson et al., 1992; Strickland et al., 1996), and a third relied on occupational information drawn from hospital charts and municipal records (Chio et al., 1991). In the only study with a more sophisticated assessment of exposure by a panel of industrial hygienists, only one of the positive associations for self-reported occupational solvent exposure was maintained (exposure to cleaning solvents and degreasers); the data did not, however, show an increased risk at higher exposure. Overall, these findings do not support an association between solvent exposure and ALS.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and amyotrophic lateral sclerosis.

Multiple Sclerosis and Solvent Exposure: Background and Epidemiologic Studies

Multiple sclerosis (MS) is a chronic and disabling neurologic disorder whose pathologic hallmark is immune-system-mediated destruction of myelin. The disorder has a marked geographic distribution. Its prevalence and incidence have been found to increase with increasing distance from the equator. The disease has a female:male ratio of about 2:1, with peak incidence between the ages of 25 and 35 years (IOM, 2001). The epidemiologic evidence points to the importance of susceptibility in adolescence and a long latency (Wolfson and Wolfson, 1993). There is some evidence, albeit weaker, that in addition to risk factors acting during the susceptibility period, there may be environmental triggers that act closer to the time of disease onset. Although the precise etiology of MS is unknown, the most widely accepted hypothesis is that early exposure to one or more viruses may initiate it (Granieri et al., 2001). More recently, smoking has been shown to be associated with an increased risk of MS (Hernan et al., 2001).

The committee reviewed four primary research articles, and it excluded results of reviews or meta-analyses of organic solvents and MS (Landtblom, 1997; Landtblom et al., 1996). An additional study was excluded (Amaducci et al., 1982) because the ascertainment of exposure to solvents was based only on occupational information obtained from census data (not from subjects themselves) and related only to the time of the census. Another study, from Denmark (Mortensen et al., 1998), was excluded because it was based on

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registry data and occupation was used as a proxy for exposure to solvents. In other words, the two studies were both excluded for lack of specificity about solvent exposure.

The remaining studies used a case–control design. Two were carried out in Sweden (Flodin et al., 1988; Landtblom et al., 1993), one in Norway (Gronning et al., 1993), and one, a twin study, in Finland (Juntunen et al., 1989) (Table 7.11). Three of the studies used the diagnostic criteria of Schumacher to identify clinically definite MS (Schumacher et al., 1965), whereas the study by Gronning and colleagues (1993) used the Bauer diagnostic criteria (Bauer, 1980). All four studies included prevalent cases.

Juntunen and colleagues (1989) studied 19 twins with MS drawn from the Finnish Twin Cohort and cross-referenced with the country's Hospital Discharge Registry. The controls were the unaffected twins, except that two of the 19 twin pairs were concordant for MS, and they were excluded from the study. The authors report collecting a "detailed history" of exposure at work, chemical compounds used, work tasks completed, working conditions, ventilation, and protective equipment used; but they give only sparse details in the publication. A "rough" classification of exposure to chemicals (including solvents) was determined as follows: 0 = no exposure, 1 = occasional exposure, and 2 = slight exposure. The precise timing of the exposure relative to disease onset is not stated. The use of only same-sex twin pairs obviated consideration of the confounding effect of age and sex, but the possible confounding effect of other exposures also was not considered. In only one twin pair had the affected twin been exposed to solvents and the unaffected not, this resulted in an OR of 0.4. In short, no association was found.

Gronning and colleagues (1993) studied 155 cases, 93% with clinical onset in Hordaland, an area of western Norway. The publication does not specify the source of cases (such as hospital records and an MS registry). The 164 controls were recruited from hospital patients with a diagnosis of traumatic fractures, traumatic rupture of ligaments, sciatica, minor plastic surgical procedures, or benign gynecologic disorders. Both cases and controls had been participants in a larger case–control study who reported ever having been active workers. The investigators assessed occupational exposure to solvents in a questionnaire about the types of exposure, frequency and duration, symptoms of intoxication, and use of protective equipment. It is not clear from the article whether the questionnaire was self-administered or interview-based. For cases, exposure occurring before the onset of MS was used for the analysis. For controls, exposure before the mean year of onset in the cases was used. In addition, exposures were quantified with an exposure index. Gronning and colleagues found no evidence to support an association between exposure to organic solvents and the occurrence of MS. Compared with no exposure, occupational exposure to solvents for 1–5 years and more than 5 years yielded ORs of 1.23 (95% CI = 0.55–2.76) and 1.97 (95% CI = 0.87–4.48), respectively. No significant associations were found with use of protective equipment, exposure to the combination of organic solvents and welding, or exposure to organic solvents and other chemical compounds.

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TABLE 7.11 Multiple Sclerosis and Solvent Exposure

Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR	Adjusted OR (95% CI or *p*)	Comments
Juntunen et al., 1989 Finland Twin study	19 twins from Finnish twin cohort (all adult, same sex); linked to hospital discharge register; Prevalent cases (1972–1985); Schumacher diagnostic criteria; checked all diagnoses	17 unaffected twins; examined carefully; two twins found to have MS	Information collected by specialist in occupational medicine; work tasks, working conditions, equipment used; 0 = no exposure, 1 = occasional exposure, 2 = slight exposure	Occupational solvent exposure	0.4 ($p > 0.1$)		Sparse on exposure methodology; Five control twins had occupational solvent exposure, but not cases
Gronning et al., 1993 Norway Subset of larger case–control study of MS	155 cases with onset from 1976–1986; diagnosed by 1986; Bauer criteria; Living in Hordaland; Prevalent cases	164 hospital patients with other diagnoses; matched on age, sex, residence	Questionnaire with specific questions on occupational exposure to solvents; Only exposures before onset; Exposure information: type, frequency, duration, symptoms of toxicity; Ravnskov method used to develop exposure index	Occupational solvent exposure Unweighted duration: 1–5 years over 5 years Exposure index: less than 2.5 over 2.5		1.55 (0.83–2.90) 1.23 (0.55–2.76) 1.97 (0.87–4.48) 1.44 (0.69–3.00 1.74 (0.72–4.25)	Logistic regression controlled for sex, age, area of residence

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Reference, Country	Cases	Controls	Exposure Determination	Solvent Exposure	OR	Adjusted OR (95% CI or *p*)	Comments
Flodin et al., 1988 Sweden	83 cases from two hospitals, diagnosed 1981–1985; sample overlaps that of Landtblom et al. (1993) Diagnostic criteria, definite per Schumacher criteria, probable-possible per Rose criteria	467 controls from cancer study; randomly drawn from population registers of hospital catchment area	Questionnaire, 10 of 17 questions on occupational exposure; minimum of 1 year of exposure required; discarded exposure information within 5 years of onset Ravnskov method for exposure index: 0 = not exposed; 4 = highest, as defined by occupation	Men: occupational solvent middle–to–high (2,3,4) vs low–to–none (0,1); Men and women: occupational solvent 2 vs 0, 1 3 vs 0, 1 4 vs 0, 1 Solvent only Solvent and welding exposure		3.1(1.4–6.8) 1.7 (0.7–4.0) 3.6 (1.2–11) 0.7 (0.05–9) 2.0 (0.9–4) 13.2 (3.4–51)	Use of Miettinen confounder score (age, sex, other exposures); also stratification by sex
Landtblom et al., 1993 Sweden	91 cases from two hospitals, diagnosed 1983–1988; sample overlaps that of Flodin et al. (1988) Diagnostic criteria same as Flodin et al. (above)	348 controls from population registers of hospital catchment area	Same as Flodin et al. (above)	Men: occupational solvent middle–to–high (2,3,4) vs low–to–none (0,1); Women: occupational solvent middle–to–high (2,3,4) vs low–to–none (0,1); Occupational solvent; logistic regression men and women men women		3.4 (1.2–9.4) 2.8 (0.9–8.0) 2.8 (1.3–5.5) 3.3 (1.1–9.5) 1.9 (0.6–5.7)	Use of Miettinen confounder score (age, sex, other exposures); also stratification by sex

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Two studies from Sweden by the same team of investigators were of largely overlapping patient populations. They recruited cases from patient files of neurology clinics and departments (Flodin et al., 1988; Landtblom et al., 1993). The major differences between the studies were the years over which cases were recruited and the method of recruiting controls. For the earlier study (Flodin et al., 1988), controls were selected from previous participants in a cancer case–control study. The controls had been randomly selected from the population registries of the counties of interest, corresponding to the catchment areas of the hospitals with the MS cases. In the later study (Landtblom et al., 1993), the population registries of the catchment areas of the hospitals were used directly. The two studies used similar methods to ascertain exposure. Questionnaires were mailed to cases and controls. More than half the questions were related to occupational exposure. Some of the questions required more-detailed responses with respect to frequency, intensity, and duration of exposure. A minimum of 1 year of exposure was required, as was a 5-year latency period (that is, exposure that took place less than 5 years before disease onset was excluded). The 5-year latency period was selected to avoid inclusion of exposures that may have been a consequence of the disease itself, such as a diagnostic x-ray exposure. Exposure to ionizing radiation was also a risk factor considered in the case–control studies. A quantitative classification was developed to describe five levels of increasing exposure based strictly on occupational category (0 = not exposed and 4 = highest intensity of exposure).

The results of the 1988 Swedish study by Flodin and colleagues indicated a strong association between occupational exposure of men to solvents and MS (OR = 3.1, 95% CI = 1.4–6.8). There was an even stronger odds ratio for leisure-time exposure to solvents and MS (OR = 16.2, 95% CI = 2.8–92), but there were only four cases and two controls, and thus a very wide confidence interval. In another analysis, the combination of occupational exposure to solvents and welding resulted in a strong association (OR = 13.2, 95% CI = 3.4–51), but no association was observed for occupational exposure to solvents alone. No significant associations were observed in women. In the second Swedish study (Landtblom et al., 1993), solvent exposure (middle to high vs low to none) resulted in a moderate association in men and women combined (OR = 2.8, 95% CI = 1.3–5.5). In women only, there was no positive association. In men only, occupational solvent exposure was associated with MS, as was exposure specifically to kerosene. The authors speculated that solvents might contribute to MS by enhancing viral entry across the blood–brain barrier into the CNS.

Summary and Conclusion

Two case–control studies found no association between occupational solvent exposure and MS (Groning et al., 1993; Juntenen et al., 1989). The two studies conducted in Sweden found some positive associations with exposure to solvents, particularly in men. Those two studies were conducted with similar methods by the same group of investigators. The exposure classification was based on occupational category without the benefit of an occupational hygienist's evaluation. No stated adjustment was performed for alcohol exposure or smoking. In addition, the timing of the exposure relative to the onset of MS is unknown, apart from its being more than 5 years before onset. Those studies raise suspicion, but they do not meet the committee's criteria for "limited/suggestive" evidence, because of the potential for bias, including confounding.

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The committee concludes, from its review of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and multiple sclerosis.

Alzheimer's Disease and Solvent Exposure: Epidemiologic Studies

Alzheimer's disease (AD), a neurodegenerative disease marked by progressive impairment in cognition and memory, is described earlier in this chapter. The committee evaluated five studies: three from the United States (Graves et al., 1998; Kukull et al., 1995 and Shalat et al., 1988), one from Canada (CSHA, 1994), and one from Australia (Gun et al., 1997) (Table 7.12).

All studies, which were case–control, included cases based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria for the diagnosis of AD (McKhann et al., 1984). This diagnostic scheme distinguishes between possible, probable, and definite AD. Definite AD can be diagnosed only pathologically through biopsy or at autopsy. Three of the studies included only probable AD, one included possible AD (Gun et al., 1997), and one (Shalat et al., 1988) did not state whether subjects with possible AD were included. Cases for four studies were recruited from medical-care settings; the other study (CSHA, 1994) recruited cases with recent onset (within 3 years) previously identified in a population-based prevalence study.

Two studies were based on the AD registry of Group Health Cooperative, a large health maintenance organization in Seattle, Washington. The first was by Kukull and colleagues (1995), and the later study (Graves et al., 1998) was restricted to a subset of cases from the Kukull et al. (1995) study for whom a spouse was available to serve as a proxy informant. That strategy was adopted to enhance the accuracy of job information. The controls in both studies were a random sample of patients from the same Group Health Cooperative from which the AD registry recruited cases. Controls were frequency-matched on age and sex, and they were included if they achieved a score of more than 28 of a possible 30 on the Mini-Mental Status Examination, a test of cognitive function. Job-history information was obtained at interview about exposure to five classes of solvents: aromatic hydrocarbons, chlorinated solvents, ketones, fuels, and alcohols.

Kukull and colleagues (1995) reported an association between occupational solvent exposure and AD in men. When exposure was defined as "exposure to any solvent" in one of the five classes, the study found, in men only, an adjusted OR of 6.3 (95% CI = 2.2–18.1). The adjusted odds ratio for both sexes was not significant. The authors speculate that underreporting by controls may have resulted in the findings of the higher association in men. When solvent exposure was defined differently, through job descriptions of four solvent-related occupations, the adjusted OR for the association between what was termed probable solvent exposure and AD was 1.8 (95% CI = 1.1–3.1).

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TABLE 7.12 Alzheimer's Disease and Solvent Exposure

Reference, Country	Cases	Controls	Exposure Determination	Exposure	Adjusted OR (95% CI)	Comments
Kukull et al., 1995 US	193 cases of probable or definite (if deceased) AD from Group Health Cooperative AD registry; Required proxy for interview	243 controls randomly sampled from same Group Health Cooperative; frequency-matched on age, sex	Interview with proxy about all jobs over 1 year since age 16 years; Considered exposure to five specific classes of solvents (aromatic hydrocarbons, chlorinated solvents, ketones, fuels, alcohol); Also asked about "probable" solvent exposure based on job descriptions of occupations (printing, asphalt-related, oils, glues, rubber production); Reference year was 1 year before onset of first symptom	Both sexes: ever (vs never) occupationally exposed to any solvent class Men only: exposure to any solvent class Women only: exposure to any solvent class	2.3 (1.1–4.7) 6.0 (2.1–17.3) 0.7 (0.2–2.1)	Adjusted for age, sex, child proxy, greater than high-school education Authors comment that underreporting by controls may have accounted for higher association in men; 15–20 years elapsed between last exposure and onset of AD
Graves et al., 1998 US	89 cases of probable AD from Group Health Cooperative AD registry; subset of Kukull et al. (1995) Required spouse informant for interview	89 controls randomly sampled from same Group Health Cooperative; frequency-matched on age, sex; Spouses both interviewed	Interview with spouse proxy about all jobs over 1 year since age 16 years; Industrial hygienist blind to case–control status rated each job for exposure to solvents; five classes of solvents (aromatic hydrocarbons, chlorinated solvents, ketones, fuels, alcohol); Rreference year was 1 year before onset of first symptom	Ever (vs never) occupationally exposed to any solvent class: Duration exposure: 1–17 years 18 or more years Age at half cumulative exposure: 1–33 years 34 or more years Low intensity × duration High intensity × duration Low intensity Moderate–high intensity	1.77 (0.8–3.9) 1.10 (0.43–2.82) 2.62 (1.07–7.43) *p*-trend = 0.03 1.20 (0.48–3.00) 2.67 (1.03–6.94) *p*-trend > 0.05 1.57 (0.62–3.96) 2.00 (0.79–5.10) 2.46 (0.92–6.57) 1.37 (0.60–3.36)	Participation by only 89 of 130 eligible cases and 89 of 166 eligible controls; Dose-response findings divergent

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Reference, Country	Cases	Controls	Exposure Determination	Exposure	Adjusted OR (95% CI)	Comments
Gun et al., 1997 Australia	170 from Sydney hospitals; possible or probable AD admitted 1986–1988; Not clear whether cases are incident or prevalent cases	170 controls recruited from same or neighboring practice; matched on age, sex; interviewed 1986–1989	Interview (blind to case–control status) of informant; complete job-history details of all jobs over 6 months; employer name, type of activity, substances handled Job–exposure matrix developed, given to panel of industrial hygienists, which estimated probability of exposure to specific chemicals by reviewing matrix, informant responses Timing of exposure not specified, but mention of subanalyses "exposure before 1980 and before 1970"	Aromatic hydrocarbons Chlorinated hydrocarbons Any hydrocarbons	1.33 (0.79–2.24) 1.86 (0.75–4.92) 1.31 (0.83–2.07)	Simulation to assess impact of information bias on exposure to aromatic hydrocarbons gave OR = 1.90 (1.23–2.96) Also looked at control–proxy agreement, estimated sensitivity with control as standard; sensitivity 0.33–0.67; proxy underestimated exposure
CSHA, 1994 Canada	258 population-based, recent-onset prevalent AD, probable only; Symptoms present not more than 3 years before study diagnosis	535 controls from prevalence study found cognitively normal on clinical examination; matched on age, study center	Self-administered risk-factor questionnaire; Proxies for cases, controls; Asked about exposures since leaving school or in adulthood	Occupational solvent Occupational glue also adjusted for education	0.76 (0.38–1.54) 2.16 (1.25–3.70) 1.80 (0.99–3.27)	Adjusted for age, sex, residence (community vs institution); Subjects older than in most other studies; Reliability of occupational-exposure information by proxy low; kappa = 0.38

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Reference, Country	Cases	Controls	Exposure Determination	Exposure	Adjusted OR (95% CI)	Comments
Shalat et al., 1988 US	98 male cases from Massachusetts veterans hospital; iagnosed 1975–1985; Unknown whether possible AD also included	162 controls from voter-registration list; matched on sex, birth year, town of residence	Mail questionnaire on previous occupation to spouse or next of kin; Exposure to organic solvents; Detailed occupation history (18 industry categories) assessed by panel of industrial hygienists blind to hypothesis; Ttiming of exposure not specified	Solvent exposure: ever over 10 years Organic-solvent exposure index	 1.0 (0.05–1.9) 0.8 (0.4–1.9) 0.9 (0.4–2.2)	Adjusted for education; Not clear how findings are related to each method of exposure assessment

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The later analysis by Graves and colleagues (1998) used a subset of the Kukull study subjects for whom spouses served as proxy informants. It diverged from the earlier study by having an industrial hygienist rate the exposure information gathered from spouse proxies (for cases and controls). The study reported that the hygienist-assessed exposure to any solvent was not associated with AD. The study examined dose–response relationships in four ways. It found a moderate association in those with 18 years or more of occupational solvent exposure (OR = 2.62, 95% CI = 1.07–7.4) and a moderate association with being 34 years old or older at half-cumulative lifetime exposure (OR = 2.67, 95% CI = 1.03–6.94). Total intensity of exposure (years on the job multiplied by intensity ratings) was not associated with AD, and intensity ratings alone resulted in a paradoxic relationship: low intensity carried higher (albeit nonsignificant) odds ratios (OR = 2.46, 95% CI = 0.92–6.57) than did moderate to high intensity (OR = 1.37, 95% CI = 0.60–3.36). On the basis of the conflicting dose–response relationships, the authors concluded that lifetime occupational exposure to solvents was not likely to be an important risk factor for AD.

Gun and colleagues (1997) compared 170 cases of possible or probable AD with controls who were recruited from the same or neighboring general practices as the cases (recruited from Sydney, Australia, hospitals) and matched on age and sex. Informants (proxies) were interviewed by trained lay interviewers and were asked to provide a complete job history. Investigators used that information to construct a job–exposure matrix. The matrix was given to a panel of occupational hygienists to generate lifetime cumulative exposure. After adjusting for family history of AD, the study did not report any significant associations between AD and occupational solvent exposure. The relevant solvent exposures listed in the study were to aromatic hydrocarbons, chlorinated hydrocarbons, and any hydrocarbons. A special analysis, however, found that the occupational-exposure information supplied by proxies underestimated exposure of controls; this suggested to the authors that the odds ratio was biased toward unity.

The Canadian Study of Health and Aging (CSHA, 1994) was a major population-based study of risk factors for AD. Cases (n = 258) were identified from subjects who were found to be suffering from AD in a national study of dementia in Canada. Controls (n = 535) were drawn at random from subjects who were found *not* to be cognitively impaired during the diagnostic clinical examination. Proxies for both cases and controls were asked about exposure, including occupational and environmental, in a risk-factor questionnaire. The study adjusted for age, sex, education, and residence in the community or institution. There was no observed association with occupational exposure to solvents. For occupational exposure to glues, in particular, the analysis found a significant association when adjusting for age, sex, and residence but the association became nonsignificant (OR = 1.8, 95% CI = 0.99–3.27) when the adjustment also included education, because lower education was a strong, independent risk factor for AD (OR = 4.00, 95% CI = 2.49–6.43). The authors report, however, that the reliability of occupational-exposure information was questionable: the kappa coefficient for the agreement between the control report and the control-proxy report of exposure to glues was only 0.38, indicating poor agreement.

Shalat and colleagues (1988) drew male cases of AD from a Massachusetts veterans hospital and compared them with controls from voter-registration lists (matched on sex, birth year, and town of residence). The investigators mailed a questionnaire to spouses or next of kin to obtain job histories and had a panel of industrial hygienists rate the degree of

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exposure. No associations were found between solvent exposure and AD after adjustment for education.

Summary and Conclusion

The evidence of an association between exposure to solvents and AD is weak. However, the very nature of the disease—late onset and dementia, leading to the need for proxy respondents—makes it extremely difficult to study the association. For the most part, the methodologic limitations in the studies (such as use of proxy respondents, lack of description of latent period, and crude measurements of exposure) most likely led to nondifferential misclassification that resulted in attenuation of odds ratios. Indeed, in some of the studies, the authors compared self-reported exposure classifications of controls with those reported by their proxies and found that the proxies generally underestimated exposure. If such findings can be generalized to proxies for cases, it would lead to underestimation of odds ratios. Several authors comment that occupational solvent exposure is most likely to occur in men, but a male-only study by Shalat and colleagues (1988) did not find a relationship, and the positive results in men were discounted by Kukull and colleagues (1995). Furthermore, population-based studies indicate that women are at greater risk for AD. In addition, the prevalence of solvent exposure in the studies evaluated here is generally low; even if there is a relationship between solvent exposure and AD, exposure is not likely to be a major contributor to the population burden of AD.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and Alzheimer's disease.

SOLVENTS AND SENSORY EFFECTS

Color Discrimination

Numerous studies have assessed color vision in workers exposed to solvents in a wide variety of occupational settings (Gobba and Cavalleri, 2000). The exposures included toluene, ethanol, perchloroethylene (tetrachloroethylene), and several solvents not relevant to the committee's mandate. Studies used the Lanthony D15 desaturated color discrimination test (Lanthony, 1978; see Appendix F for background on this test). Several of the studies found subclinical impairments in color discrimination (clinically overt color-vision loss is known as dyschromatopsia), but the occupational exposures were both current and past. The combined nature of the exposure makes it difficult to distinguish whether the effect was short-term or long-term. The elapsed time between the most recent exposure and color-vision testing ranged from unstated (Baird et al., 1994; Mergler et al., 1988; Semple et al., 2000; Valic et al., 1997) through about 16 hours (Blain et al., 1985; Cavalleri et al., 1994, 2000; Gonzalez et al., 1998; Mergler and Blain, 1987; Mergler et al., 1987; Muttray et al., 1997, 1999; Zavalić et al., 1996, 1998a,b,c) to about 60 hours (Muttray et al., 1995). These cross-sectional studies were thus not designed to examine whether effects on color discrimination were long-term or short-term.

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A longitudinal study of dry-cleaning workers exposed to perchloroethylene (tetrachloroethylene) found that over a 2-year period color-vision discrimination worsened with increased exposure and did not decline in workers whose exposure was reduced (Gobba et al., 1998). However, because the study did not have an exposure-free interval before vision testing, its results do not bear on the question of whether tetrachloroethylene's effects were short-term or long-term.

The only studies with an exposure-free interval were of styrene, a solvent not reported to have been sent to the Gulf War. After an exposure-free interval of 1 month, styrene's effects on color discrimination were mixed: one study showed a positive result, and the other showed recovery (Gobba and Cavalleri, 2000). Thus, none of the published studies shed light on the question of whether exposure to relevant solvents is associated with long-term effects on color vision.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and a long-term reduction in color discrimination.

Hearing Loss

Occupational noise is the most common cause of noise-induced hearing loss (Sataloff and Sataloff, 1993). In about 40% of the 28 million people in the United States with hearing loss, the loss is partly attributable to exposure to loud sounds. Noise-induced hearing loss can be severe and permanent, but it is entirely preventable.

Two types of hearing loss can occur—conductive and sensorineural—depending on which parts of the ear and nerve pathways are affected. Conductive hearing loss is caused when the conduction of sound from the outer to the inner ear is blocked. The causes include middle ear infections, collection of fluid or wax in the ear, damage to the eardrum by infection or trauma, otosclerosis, and, rarely, rheumatoid arthritis that affects the joints between the ossicles (Sataloff and Sataloff, 1993).

Sensorineural hearing loss involves damage to the pathway for sound impulses from the cochlea to the auditory nerve and the brain. The causes include age; damage to the cochlea caused by loud noise; viral infection; Meniere's disease (abnormal pressure in the inner ear); some drugs, such as aspirin, quinine, and some antibiotics, which can affect the hair cells; acoustic neuroma; meningitis; encephalitis; multiple sclerosis; brain tumors; and strokes (Sataloff and Sataloff, 1993).

In 1986, a longitudinal study reported a higher prevalence of hearing disability in workers with both solvent and noise exposure than in workers at the same facility exposed only to noise (Bergström and Nyström, 1986). Several studies have since examined the relationship between simultaneous exposure to solvents and noise and the occurrence of hearing impairment. Morata and colleagues (1993, 1997a,b) performed audiometry (see Appendix F) in three studies of current workers exposed to noise and mixed solvents, including toluene. Two studies (Morata et al., 1993, 1997b) found mild hearing loss with mixed solvent exposure (but it is not clear whether the population was the same for both studies). In one of those studies, Morata et al. (1993) also found that the risks were greater with combined noise and toluene exposure than with noise alone or mixed solvents alone. The other of the three studies (Morata et al., 1997a) found hearing loss in petroleum-refinery

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workers in South America, but the study did not make adjustments for alcohol use or smoking and had much more limited exposure information.

Despite the positive findings in those studies, it is not known whether the hearing loss was short-term or long-term, because none of the studies included an exposure-free interval before testing. The short-term nature of the effect is suggested by two lines of evidence from the studies themselves: the correlation between hearing loss and the concentrations of urine biomarkers for solvent exposure (Morata et al, 1997b) and the lack of an association with employment duration in two of the studies (Morata et al., 1993, 1997b). The committee did not identify any epidemiologic studies of relevant solvent exposure and hearing loss with an exposure-free interval.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and long-term hearing loss.

Olfactory Function

Schwartz and co-workers (1990) reported a strong association between current solvent exposures at two paint-manufacturing plants and impaired olfactory function as measured by the University of Pennsylvania Smell Identification Test. A cross-sectional study of current painters, however, found no association with impaired olfactory function on the test (Sandmark et al., 1989); the authors suggested that because some painters had had much greater exposures in the past, any solvent effect on olfactory function is likely to be reversible. A third cross-sectional study of workers exposed primarily to toluene (Hotz et al., 1992) also reported associations with self-reported smell and taste problems that appeared to be temporary and reversible. The committee did not identify any studies with an exposure-free interval.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposures to the solvents under review and long-term reduction in olfactory function.

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8

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Evaluating toxicologic impacts upon the reproductive process requires consideration of the mother, father, and fetus/offspring. A toxic insult may be sustained by either the father or mother prior to conception or by the mother and fetus during gestation with results that might not be detected until considerably after the child's birth. Potential effects may be observed over an extended period of time from before conception to after birth.

In the male, sperm undergo a three-month maturation cycle during which they might receive an acute insult, which could interfere with their successfully fertilizing an ovum to produce a healthy fetus. Of more concern here is that exposures incurred more than a decade ago during the Gulf War may have produced persisting damage that could impair reproduction. Similarly, in the female, exposure of the maturing ovum in a given menstrual cycle or of a developing fetus might cause immediate damage that will be realized within that reproductive cycle. The adverse effect might be a transient event like a spontaneous abortion or, in the case of a congenital malformation, a permanent condition for the offspring. Inasmuch as there were more women serving in the Persian Gulf, the issue of adverse reproductive effects in exposed women is of more concern than it has been in previous conflicts. The occurrence of pregnancy was reason for immediate evacuation from the area. The committee was concerned that toxic exposures during the earliest period of gestation (when pregnancy may have not yet have been recognized) might pose a threat to the developing fetus. The committee considered whether possible exposures might have produced a lasting impact on the reproductive capacity of both male and female Gulf War veterans.

Most research on reproductive toxicity has focused on exposures occurring just prior to conception or during gestation. Animal toxicology studies can be much more specific about timing of exposure with respect to conception than is possible in epidemiology studies. Few epidemiology studies have focused specifically on delayed reproductive effects as was the committee's main concern, but some studies will span a long enough observation period to include such events. Furthermore, the short-term responsiveness of the male and female reproductive systems to toxic insults provides an indication of whether any effect that might be persistent is plausible. This chapter discusses studies of maternal and paternal exposure to insecticides and solvents that have examined several reproductive end points, grouped below according to whether they occur prior to conception (sperm morphology, infertility, and hormonal changes), during pregnancy (fetal loss), or as congenital malformations (following birth).

PRECONCEPTION

Conception entails the fertilization of a healthy ovum by a functional sperm. Female gametes are not readily observable, but the accessibility of semen provides an indirect means of

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evaluating the male reproductive system. Traditionally measured characteristics of semen samples include sperm concentration, motility, and structure. Oligospermia is defined as sperm concentration below the reference value of 20 million sperm/mL, asthenospermia as less than 50% motile sperm with forward progression, and teratospermia as less than 30% sperm with normal head structure (Rowe et al., 1993). A number of factors may adversely influence male fertility, including sexually transmitted and other diseases (such as diabetes, tuberculosis, and mumps), prolonged high fever, some drugs and medications (such as hormone treatments and cimetidine), some injuries, and some occupational exposures (such as to lead and to the pesticide dibromochloropropane) (Rowe et al., 1993). Another means of indirectly evaluating the impact of potentially toxic exposures on reproductive health is to assess hormone levels in either male or female subjects.

Infertility is the failure to conceive after at least 12 months of unprotected intercourse (Rowe et al., 1993). It has been estimated that 10–15% of couples of reproductive age experience some form of infertility (Speroff et al., 1999). In the general population, the probability that a couple engaging in unprotected intercourse will conceive in the first month is 30%; about half of all couples will conceive within 2 months, and 80% in 6 months (Joffe, 1997). There are numerous risk factors for infertility, including advanced age and obesity in women; previous reproductive experiences; genetic factors; diseases such as chlamydial infection in women or epididymitis in men; and, to a lesser extent, cigarette smoking, alcohol consumption, and toxic agents in environmental and occupational settings in either sex (Templeton, 2000).

A frequently used measure of infertility is time-to-pregnancy (TTP). TTP studies examine the number of months or menstrual cycles that are required to conceive. The results of TTP studies are often expressed as fecundability ratios. Fecundability refers to the probability of conceiving within one menstrual cycle and is a population-based measure that is useful in the quantitative analysis of fertility potential (Speroff et al., 1999). A fecundability ratio (FR) is the ratio of the probability of conception in an exposed group with that in a comparison group. Decreases in the fecundability ratio indicate longer time to pregnancy for the exposed group. Some studies use a conditional fecundability ratio (CFR), which includes only couples that have conceived a child.

Epidemiologic Studies of Preconception End Points and Exposure to Insecticides

Sperm and Semen Characteristics

Only a few studies have examined the relationship between insecticide use and semen characteristics. Two cross-sectional studies were conducted on a small cohort of men who were employed for 1–8 years in a carbaryl production and packaging plant. In the first study, by Whorton and colleagues (1979), 47 current and past carbaryl workers with at least 1 year of work in carbaryl production and packaging were compared with a control group of 90 male chemical-plant workers. The carbaryl-plant workers were divided into three exposure groups (high, medium, and low exposure) on the basis of frequency of exposure and job classification. Each participant was interviewed, provided a semen sample, and underwent a physical examination. The study found a greater proportion of oligospermic men among the carbaryl workers than among the chemical workers (14.9% and 5.5%, respectively, $p = 0.07$). In further analyses by job classification and exposure group, the study found that 16% of the 25 men in the high-exposure group were oligospermic, compared with 13.6% of the 22 men in the low- and medium-exposure

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groups. Among the 29 currently exposed workers, 17.2% were oligospermic, compared with 11.1% of the 18 previously exposed workers. The study provides some evidence of an increased risk of oligospermia with carbaryl exposure. The proportion of oligospermic men among the carbaryl workers was nearly three times the proportion among the controls, and there was some evidence of an association with increased exposure. Because 29 of the carbaryl workers were currently exposed to carbaryl, it was not possible to determine whether oligospermia was a long-term outcome that would persist after cessation of exposure. Furthermore, the use of chemical workers as comparison subjects might mask an effect if they were exposed to spermatotoxic chemicals.

A second study of the same carbaryl workers (Wyrobek et al., 1981) examined the relationship between sperm shape abnormalities and exposure to carbaryl. When it was possible, the same semen samples were used in both studies. However, instead of using chemical workers as the control population, this study used newly hired workers at the carbaryl plant; those men provided semen samples at their pre-employment medical examination. Workers were assigned to one of three exposure groups on the basis of the type of job held during the preceding year: nonexposed (new hires), low dose, and high dose. For morphologic analyses, 500 sperm for each person were scored, with blinding as to exposure status. As in the study by Whorton and colleagues, the control group of new hires had a lower proportion (two of 34, or 5.9%) of oligospermic men than did the carbaryl production workers (seven of 48, or 14.6%). Morphological analyses showed increases in the proportion of abnormal sperm among the carbaryl workers (52% of 30 currently exposed and 50% of 18 previously exposed) versus the new hires (42% of 34); the results were similar after stratification on potential confounders, such as smoking, medical history, or previous exposure to hazardous agents. The proportion of men classified as teratospermic (defined in this study as having more than 60% abnormal sperm) was higher in the carbaryl workers than in the comparison group (14 of 49, or 28.6%, and four of 34, or 11.8%, respectively). A dose–response relationship was not found, although the measure of exposure was rather crude for such a determination. An inverse association between number of years worked with carbaryl and percentage of abnormal sperm was found; this was opposite the direction that was expected and could not be explained by the authors. Furthermore, it was expected that there would be differences due to age; however, among the carbaryl workers, the relationship between age and percentage of abnormal structure was opposite what was expected, in that younger men had a higher percentage of sperm abnormalities.

Several studies have examined the relationship between semen characteristics and exposure to broader categories of pesticides. Larsen and colleagues (1998a, 1999) studied traditional and organic farmers in Denmark and did not find an association between pesticide spraying and adverse effects on sperm concentration, motility, or morphology. The studies were prospective and controlled for several potential confounders including the period of abstinence and the delay from sample collection to analysis.

In a cross-sectional study on testicular function in 122 workers in ornamental-flower greenhouses, expert judgment was used to categorize workers into high-, medium-, and low-exposure groups (Abell et al., 2000a). The median sperm concentration and the median proportion of normal sperm were 60% and 14% lower, respectively, in the group with high estimated dermal exposure (n = 13) than in the group with low estimated dermal exposure (n = 44). Those differences remained after adjustment for potential confounders. However, the relevance of this study for the purposes of this report is limited by the exposure of the workers to more than 60 pesticides, including a number of fungicides.

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Two studies examined men in couples seeking infertility treatment at clinics in the Netherlands (Tielemans et al., 1999) and Argentina (Oliva et al., 2001). Tielemans and colleagues found an increased, but imprecise association between abnormal semen characteristics and self-reports of occupational use of insecticides (odds ratio [OR] = 1.52, 95% confidence interval [CI] = 0.33–7.06). Using a broad exposure category that grouped all pesticide exposures, Oliva and colleagues found associations between pesticide use and several sperm characteristics, including reduced motility and abnormal structure. Because of their broad definitions of pesticide exposure, these two studies do not provide specific insight into the relationship between insecticides under consideration exposure and sperm characteristics.

Additional Indirect Studies of Infertility

A case–control study of Danish couples undergoing infertility examinations used mailed questionnaires about occupational exposure (Rachootin and Olsen, 1983). Information on occupational exposures was gathered from an original sample of 927 infertile and 3728 control couples (selected from couples who had a healthy child born at the same hospital). Subgroups of couples with at least one year's infertility were defined on the basis of explanations for the subfecundity: men with sperm abnormalities (n = 258), women with hormonal disturbances (n = 305, 48 of whom had husbands with sperm abnormalities), or women or men from 129 couples with idiopathic infertility. Pesticide exposure was not more frequent in any of these subgroups as compared to their respective fertile controls.

Several studies have examined the effects of insecticide exposure on reproductive hormones. In a lindane-producing factory, Tomczak and colleagues (1981) conducted a cross-sectional study of 54 male workers (85% participation rate) and 20 clerks (unexposed external comparison group). The analysis of blood samples found elevated serum luteinizing hormone (LH) concentrations, somewhat elevated levels of follicle stimulating hormone (FSH), and somewhat depressed testosterone levels in the exposed workers. Straube and colleagues (1999) found similar results in a prospective followup study of 67 professional pesticide applicators (studied before, during, and after applying pesticides) and 125 comparison subjects. Although those studies found minor alterations in serum hormones, the clinical significance, if any, of these hormonal alterations is unclear.

Infertility

Fertility can be measured directly by determining delays in conception for couples attempting to conceive. Maternal, paternal, or couple-related exposure may be the focus of infertility studies evaluating time-to-pregnancy (TTP). As part of the Ontario Farm Family Health Study, Curtis and colleagues (1999) conducted a retrospective cohort TTP study that examined pesticide use by farm couples in Ontario, Canada. Of 2946 eligible couples, 1898 (64%) completed three mailed questionnaires; of the responders, 1048 couples with 2012 pregnancies were eligible for inclusion in the analysis. Each couple was asked to construct a monthly pesticide-use history for the year 1991 and to provide details on the pesticides used on the farm. Exposure was defined as pesticide use during the month of attempted conception or at any time during the previous 2 months (to allow residual effects of pesticide exposure on spermatogenesis). Information was collected separately for wives and husbands on monthly participation in direct pesticide use (such as mixing and application). Extensive data on potentially confounding variables were also obtained. The study found that there was no strong overall pattern of association between TTP and exposure to insecticides or other pesticides.

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There was a suggestion of decreased fecundability (increased TTP) when the women used organophosphates (CFR = 0.75, 95% CI = 0.51–1.10), carbaryl (CFR = 0.97, 95% CI = 0.63–1.49), and several herbicides. For insecticides as a group, however, the women's CFR was 1.02 (95% CI = 0.76–1.37). The CFRs were close to unity for the periods in which only the men used insecticides (CFR = 1.01, 95% CI = 0.87–1.17), carbaryl (CFR = 1.03, 95% CI = 0.84–1.26), or organophosphates (CFR = 1.04, 95% CI = 0.89–1.22). A major strength of the study is the detailed information on specific pesticides. The inclusion of all pregnancies for each couple is problematic, although the authors report that an analysis restricted to first pregnancies did not alter the results. The fact that pesticide use was highly correlated between members of a couple makes it difficult to determine whether any observed effect was specifically maternally or paternally mediated.

Other studies of TTP examined pesticides in general and did not provide specific information on insecticides. Abell and colleagues (2000b) evaluated a cohort of Danish women who worked in flower greenhouses where there was extensive use of pesticides (primarily insecticides, fungicides, and growth regulators). When overall pesticide exposure was analyzed with control for maternal and paternal smoking, maternal age, parity, and other factors, a slightly increased fecundability ratio (decreased TTP) was observed (FR = 1.11, 95% CI = 0.90–1.36). However, conception was delayed among the workers who did not use gloves (FR = 0.67, 95% CI = 0.46–0.98) and among those in the high exposure group (FR = 0.64, 95% CI = 0.45–0.90). The study did not examine specific pesticides, and it lacked paternal-exposure information, but it is important to note that the exposed group was not exposed to herbicides.

Several studies have examined paternally mediated associations between pesticide exposure and TTP. A study by de Cock and colleagues (1994) examined a population of Dutch fruit-growers; 43 couples with 91 pregnancies were eligible for the analysis. There was an association between longer TTP and application of pesticides solely by the farm owner (FR = 0.46, 95% CI = 0.28–0.77); in addition, delays in time to conception were noted during the spraying season (FR = 0.42, 95% CI = 0.20–0.92). This study is limited for the purposes of this review by the crude measure of pesticide exposure and the lack of information on the specific insecticides used.

Larsen and colleagues (1998b) examined TTP and exposure to pesticides in Danish male farmers. The study did not find differences in TTP when comparing traditional farmers (who sprayed pesticides) with organic farmers (FR = 1.03, 95% CI = 0.75–1.40). Similarly, none of the specific characteristics of pesticide use (such as cumulative years of spraying and type of equipment used) was associated with TTP.

Thonneau and colleagues (1999) investigated TTP in a group of male farmers and agricultural workers in Denmark and France. In France, 142 exposed and 220 nonexposed workers were examined, while in Denmark, the corresponding numbers were 447 and 123. The fecundability ratios did not differ between exposed and unexposed workers. However, the crude nature of the exposure measure and the problems associated with the definition of exposure limit the interpretation of the data.

Summary and Conclusion

In reviewing the studies on indirect measures of fertility, the committee did not find strong evidence of association with exposure to insecticides (Table 8.1). The studies of semen characteristics by Whorton and Wyrobek and colleagues provide limited evidence of an association between current work in carbaryl production and oligospermia and teratospermia.

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However, the studies were cross-sectional and reported on results in workers who, for the most part, were currently exposed to carbaryl, so it is unclear whether the response would persist after cessation of exposure. Two studies found altered hormonal status in individuals with pesticide exposure, but the clinical significance of the findings and whether they persist after exposure were not determined.

Only one of the TTP studies provided an analysis of specific insecticide use (Curtis et al., 1999) (Table 8.2). It did not show delayed TTP for either maternal or paternal exposure, although there was a suggestion of delayed time to conception for women who used organophosphates and carbaryl. Other studies considered pesticide exposures that were too broad for the purposes of this review.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and male or female infertility after cessation of exposure.

TABLE 8.1 Selected Epidemiologic Studies: Sperm and Semen Parameters and Exposure to Carbaryl

Reference	Population	*N*	Results (% with oligospermia or teratospermia)
Whorton et al., 1979	Carbaryl production workers		
	Oligospermia		
	Carbaryl workers	47	14.9[a]
	Current carbaryl workers	29	17.2
	Previous carbaryl workers	18	11.1
	Chemical-worker controls	90	5.5[a]
Wyrobek et al., 1981	Carbaryl production workers		
	Oligospermia		
	Carbaryl workers	48	14.6
	New-hire controls	34	5.9
	Teratospermia		
	Carbaryl workers	49	28.6
	New-hire controls	34	11.8

[a]The comparison of carbaryl workers with controls resulted in a p value of 0.07. No further comparisons were presented.

TABLE 8.2 Selected Epidemiologic Studies: Time-to-Pregnancy and Exposure to Insecticides

Reference	Population	Number of Exposure Intervals[a]	Fecundability Ratio (95% CI)
Curtis et al., 1999	Ontario farm couples		
	Insecticides		
	Females	111	1.02 (0.76–1.37)
	Males	744	1.01 (0.87–1.17)
	Organophosphates		
	Females	89	0.75 (0.51–1.10)
	Males	391	1.04 (0.89–1.22)
	Carbaryl		
	Females	51	0.97 (0.63–1.49)
	Males	214	1.03 (0.84–1.26)

[a]Number of 3-month exposure windows in which the man or woman reported pesticide use.

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Epidemiologic Studies of Preconception End Points and Exposure to Organic Solvents

Sperm and Semen Characteristics

Many studies have examined the relationship between occupational exposures and male infertility. Often, work in a specific industry was used as a surrogate for solvent exposure. In some industries (such as dry cleaning), a fairly consistent set of compounds is used, while in other industries (such as leatherwork or shoemaking), workers might be exposed to more ill-defined, heterogeneous groups of compounds. The committee's review focused on studies with well-characterized solvent exposure and adequate participation rates. A number of other studies were examined, but had limitations for the purposes of this review (e.g., Chia et al., 1994, 1996; De Celis et al., 2000; Eskenazi et al., 1991; Kurinczuk and Clarke, 2001; Rendon et al., 1994; Xiao et al., 2001).

Lemasters and colleagues (1999) achieved a high participation rate (79.5%) in a prospective longitudinal study of a group of 50 aircraft-maintenance personnel. Subjects were evaluated before first exposure to solvents and then 15 and 30 weeks after exposure had begun. The study included quantitative measurement of exposure to solvents (for example, breath-sampling and industrial-hygiene monitoring) in the interval prior to sperm collection. The average industrial exposures were less than 10% of the Occupational Safety and Health Administration personal exposure limits. The analysis controlled for risk factors for semen abnormalities (such as medication use). Exposure to solvents, defined by work area and personal measurements, was not associated with any decline below normal limits in the measures of semen quality as defined by WHO reference values (WHO, 1999). Job status correlated with several semen characteristics, but there was not a consistent pattern of association. For example, sheet metal workers had higher levels of exposure to fuels and solvents (measured in expired breath) compared with aircraft painters and had decreased sperm directional movement ($p = 0.03$); the painters had greater declines in sperm motility (19.5%, $p = 0.04$) as compared with sheet metal workers (3.2%). Given the multiple comparisons and the fact that the semen analysis results were mostly within normal ranges, these conflicting results are even less suggestive of an association between exposure to solvents and semen characteristics.

A case–control study in the Netherlands examined the relationship between occupational exposures and semen characteristics in the male partners of couples that had an infertility consultation (Tielemans et al., 1999). The 899 participants were asked to provide a semen sample and to complete detailed questionnaires regarding their occupational history. A job–exposure matrix was used to assess and verify exposures, and subjects who were exposed or nonexposed to the various chemical agent groups were compared. Changes in semen parameters were not found to be associated with exposure to organic solvents as a general category when evaluated in the total population (OR = 0.98, 95% CI = 0.60–1.59) or in men with primary infertility[1] (OR = 1.15, 95% CI = 0.66–1.99). The results for exposure to aliphatic and halogenated solvents were similar when analyzed in the total population or in men with primary infertility. Exposure to aromatic solvents showed an increased risk of abnormal semen parameters in men with primary infertility, based on 49 exposed cases (OR = 1.92, 95% CI = 0.88–4.19).

[1]Primary infertility describes the fertility status of a couple that has not conceived after a minimum of 1 year of unprotected intercourse. Secondary infertility describes the condition of a couple that has conceived but is not able to conceive again (NLM, 2002).

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Cherry and colleagues (2001) reported on two studies in Canada, one using records of couples attending a fertility clinic in Montreal in 1972–1991, and the other using records from other clinics across Canada (1984–1987). For both studies, semen samples were collected from over 80% of participants. For jobs indicating manual work, investigators used self-reported occupational title and a job–exposure matrix to classify job titles by intensity of exposure to organic solvents. In the Montreal study, among 656 males, there was an increased risk of low-active sperm count (less than 12×10^6/mL) with high exposure to solvents (OR = 3.83, 95% CI = 1.37–10.65) and moderate exposure (OR = 2.07, 95% CI = 1.24–3.44), adjusted for confounders, including age and occupational exposure to lead. The second study found a strong association only in the men with high exposure to solvents (OR = 2.90, 95% CI = 1.01–8.34). The authors acknowledged that the Montreal study spanned a 20-year period and that changes in the type and intensity of exposures over this period might lead to confounding by calendar time. However, for confounding by time to occur, there would need to be a time trend in semen parameters.

Oliva and colleagues (2001) examined occupational exposures in relationship to semen characteristics among 177 Argentinean men recruited from 253 couples that were having their first infertility consultation. Occupational history was taken by interview, and semen samples were collected. Of the participants, 22 were classified as exposed to solvents. In a comparison among all study subjects, the study found associations between solvent exposure and several measures of abnormal semen characteristics (based on WHO guidelines), including sperm concentration (OR = 2.7, 95% CI = 0.9–8.3), sperm structure (OR = 3.0, 95% CI = 1.0–9.0), and sperm motility (OR = 3.1, 95% CI = 1.0–9.5). Sperm motility was most impaired in those with primary infertility and solvent exposure (OR = 10.6, 95% CI = 1.1–105.6). This finding may be confounded because the 10 solvent-exposed cases were mostly mechanics and so might have had other exposures in common.

Rasmussen and colleagues (1988) studied metal workers exposed to trichloroethylene and found no association between exposure and semen characteristics. The study had low statistical power inasmuch as it was based on only 15 subjects.

Exposure to ethylene glycol ethers has been examined in several studies of semen characteristics. These chemicals are of concern because evidence from animal studies shows that the metabolites of ethylene glycol ethers are associated with impaired fertility characterized by testicular atrophy, abnormal sperm morphology, and decreased sperm motility (Bruckner and Warren, 2001). In a case–control study, Veulemans and colleagues (1993) examined the associations between the presence of the urinary metabolites of ethylene glycol ethers (methoxyacetic acid, or MAA, and ethoxyacetic acid, or EAA) and a diagnosis of infertility or differences in semen characteristics. They also assessed a variety of occupational exposures. The study involved 1019 men who had been clinically diagnosed as infertile or subfertile; controls were 475 male patients of the same clinic for reproductive disorders who were diagnosed as fertile. A comparison of cases and controls found inconsistent results for exposure to degreasers or cleaning products (OR = 0.89), paint removers (OR = 1.56), and solvents (OR = 0.87). Urinary EAA was detected in 45 participants, of whom 29 reported occupational exposure to solvent-related products. The study did not find an association between urinary EAA and abnormal semen characteristics; the authors speculated that might be due to a latent period between exposure and the time when observable effects are seen.

Ratcliffe and colleagues (1989) studied semen quality in 37 workers exposed to 2-ethoxyethanol (ethylene glycol monoethyl ether) at a metal-casting company and in 39 nonexposed workers from other locations in the same plant. The study found decreases in mean

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sperm count in the exposed workers but no marked changes in sperm motility, structure, or velocity or in testicular volume after adjustments for many potential confounders, including alcohol and tobacco consumption, sexual abstinence, and urogenital or other medical disorders. There was a possibility of selection bias because the participation rate among exposed workers was 50%, and the study had low statistical power.

A study of shipyard painters by Welch and colleagues (1988) examined potential exposure to the ethylene glycol ethers, 2-ethoxyethanol, and 2-methoxyethanol. An industrial-hygiene survey of the worksite measured exposures to ethylene glycol ethers and other compounds. The study examined semen samples from 73 painters (a 50% participation rate) and 40 controls and found that the painters had a higher prevalence of oligospermia and azoospermia. An analysis controlling for smoking found a higher risk of decreased sperm count per ejaculate in the exposed group (OR = 1.85, 95% CI = 0.6–5.6). No important differences were found in sperm structure, motility, or viability.

Additional Indirect Studies of Infertility

Studies have examined other indirect end points of infertility. Most are cross-sectional, and participants have continuing solvent exposure; those characteristics limit the studies' ability to inform the discussion of persistent effects. The effect of solvent exposure on women's menstrual cycles has been examined in several studies, including a cross-sectional study of women working in a factory who were exposed to toluene in the manufacture of audio speakers (Ng et al., 1992). The frequency of dysmenorrhea (painful menstruation) was higher in the high-exposure group (15.6%) and in the low-exposure group (13.8%) than in the community control group (3.2%). A study of 1408 female workers in petroleum and chemical processing plants in Beijing, China, found a consistent association between exposure to aromatic solvents and abnormal menstrual-cycle length, but the exposure and health-outcomes assessments were limited and there was potential for confounding by other chemical exposures (Cho et al., 2001). Other studies of menstrual disorders have had inconsistent results (Georgieva et al., 1998; Gold et al., 1995; Zielhuis et al., 1989).

In a case–control study of Danish couples, Rachootin and Olsen (1983) compared the male or female occupational exposures of subfecund subgroups (with sperm- or hormone-related reasons for infertility or idiopathic infertility) with those of fertile control couples. (The derivation of the subgroups was described above where this study was considered with respect to pesticides.) The participants completed a questionnaire asking about occupational exposures, which included degreasers, dry-cleaning chemicals, and other organic solvents. Among the many comparisons, the only suggestive association was for women with idiopathic infertility and exposure to dry-cleaning chemicals (OR = 2.7, 95% CI = 1.0–7.1), adjusted for age, education, residence, and parity.

Several cross-sectional studies have examined the effects of solvents on reproductive hormones. Svensson and colleagues (1992a,b) found that exposure to toluene was associated with lower blood concentrations of FSH, LH, prolactin, and testosterone in young male rotogravure printers when compared with factory workers. The authors state that the effects may be transitory, since a reversal of the decreases in LH and FSH levels was seen in a subset of the printers after a 4-week exposure-free period. Studies of exposure to trichloroethylene among 85 male workers found moderate decreases in FSH and testosterone, and stronger increases in dehydroepiandrosterone sulfate with increasing duration of exposure (Chia et al., 1997; Goh et al., 1998). Those studies were relatively small and had little or no control for important

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confounders (such as alcohol use). No adverse clinical consequences were reported. Oliva and colleagues (2001) also found lower LH concentrations in men exposed to solvents who were seeking infertility treatment.

Infertility

Several studies have examined the effects of solvent exposure on infertility by studying TTP. In a cross-sectional study, Plenge-Bonig and Karmaus (1999) examined infertility in printing-industry workers. The workers (150 men and 90 women) were interviewed about their occupational and reproductive histories, and their exposure to toluene was categorized according to job descriptions and previous measurements by industrial hygienists. The study did not find an effect on TTP in the men who were exposed to toluene (FR = 1.05, 95% CI = 0.93–1.19); there was no relation to exposure category (none, low, medium, or high). The analysis of exposed female workers found increased TTP (FR = 0.52, 95% CI = 0.28–0.99). The study controlled for such confounders as age, ethnicity, smoking, parity, and frequency of sexual intercourse. The participation rates were low (50% in men and 39% in women) and may have involved bias by self-selection.

Sallmen and colleagues conducted two studies on TTP. The first (Sallmen et al., 1995) examined women who had been biologically monitored for exposure to organic solvents at the Finnish Institute of Occupational Health. The participants were asked about a number of occupational and environmental factors, including work history and possible solvent exposure in the 12 months before pregnancy. Using a fecundability measure termed the incidence density ratio (IDR), this study controlled for a number of confounders and found reductions in fecundability in the groups with high (IDR = 0.41, 95% CI = 0.27–0.62) and low solvent exposure (IDR = 0.69, 95% CI = 0.48–0.99). Exposures to high levels of specific solvents were found to reduce fecundability with imprecise risk estimates (trichloroethylene, IDR = 0.61, 95% CI = 0.28–1.33; tetracholoroethylene, IDR = 0.69, 95% CI = 0.31–1.52).

In the second study, Sallmen and colleagues (1998) looked at TTP among couples in which the man had been monitored for organic solvent exposure at the same Finnish institute. The questionnaire on reproductive history was returned by 316 of the 438 wives of the men (72% participation rate); the final study population consisted of 282 couples after exclusions. Biologic measurements of exposure were available for 69% of those men and were used to supplement self-reported information on occupational exposures. The study found an adjusted fecundability measure (fecundability density ratio [FDR]) of 0.80 (95% CI = 0.57–1.11) for high or frequent paternal exposure and a similar result for low or intermediate exposure (FDR = 0.74, 95% CI = 0.51–1.06). Nor did this study find effects on TTP for specific solvent exposures; for example, for intermediate/high exposure to trichloroethylene the investigators found an FDR of 1.03 (95% CI = 0.60–1.76).

Several studies have examined the reproductive histories of semiconductor workers with a focus on exposure to ethylene glycol ethers. Samuels and colleagues (1995) conducted a study of fertility among men working in eight semiconductor-manufacturing companies (1984–1989). They used the workers' current jobs to define exposure status, first dichotomizing among fabrication workers (n = 241) and nonfabrication workers (n = 447) and then subdividing the fabrication workers by types of work processes. The study did not find increases in TTP when fabrication and nonfabrication workers were compared (adjusted FR = 0.98, 95% CI = 0.80–1.19). Fecundability was also not reduced in the subanalysis of the workers (adjusted FR = 1.03,

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95% CI = 0.70–1.51) in whom exposure to ethylene glycol ethers was of particular concern (those involved in masking work—etching and photolithography).

A prospective study (Eskenazi et al., 1995a) asked female semiconductor workers to complete a daily diary on reproductive history and occupational exposures and to collect a daily urine sample for 6 months. As in the previous study, fabrication and nonfabrication workers and subgroups of fabrication workers were compared. Extensive analysis, adjusting for a number of confounders, found reduced fecundability (increased TTP) in fabrication workers (FR = 0.69, 95% CI = 0.38–1.25) with adjustments for recent pregnancy or lactation. In workers exposed to ethylene glycol ethers (259 cycles), there was also a longer TTP (FR = 0.37, 95% CI = 0.11–1.19).

Several studies of infertility used measures other than TTP. Correa and colleagues (1996) examined the extent of subfertility (taking more than 1 year to conceive) related to 561 pregnancies of female workers and 589 pregnancies of wives of male workers at two semiconductor manufacturing plants in the eastern United States. Reproductive and occupational histories were obtained through interviews; company records were used to develop matrices of industrial processes and to differentiate potential exposure to ethylene glycol ethers and their acetates. In female employees, of whom only six were exposed, there was a increased risk (OR = 4.6, 95% CI = 1.6–13.3). Among spouses of male employees with high potential exposure to ethylene glycol ethers the risk of subfertility was elevated (OR = 1.7; 95% CI = 0.7–4.3). A study of solvent-exposed male workers at an Italian mint (Figa-Talamanca et al., 2000) also found an elevation in the risk of conception delay of more than 6 months (OR = 1.69, 95% CI = 0.62–4.62); this was based on a small number of cases.

Summary and Conclusion

Although a number of studies have examined the potential effects of occupational exposure to solvents on semen characteristics, few studies have investigated persistent effects after cessation of solvent exposure. There is evidence from animal studies that exposure to specific solvents, particularly ethylene glycol ethers, is associated with testicular atrophy, decreased sperm motility, and abnormal sperm structure (Bruckner and Warren, 2001). Data on the effects of human exposure to ethylene glycol ethers also show associations with several semen parameters but are insufficient to conclude that the effects would persist after exposure ceases.

Studies of TTP and other measures of infertility have found inconsistent associations with exposure to solvents regarding paternal exposures (Table 8.3). Increased TTP was seen in several studies of maternal exposures to solvents. No studies have examined the presence or absence of persistent effects on fertility once exposure ceases.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to specific organic solvents under review or solvent mixtures and male or female infertility after cessation of exposure.

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TABLE 8.3 Selected Epidemiologic Studies: Time-to-Pregnancy and Exposure to Organic Solvents

Reference	Population	Number of Pregnancies	Fecundability Ratio (95% CI)
Toluene			
Plenge-Bonig and Karmaus, 1999	Printing-industry workers in Germany		
	Female employees	89	0.52 (0.28–0.99)
	Male employees	16	1.05 (0.93–1.19)
Solvents			
Sallmen et al., 1995	Female workers in Finland	197	
	High exposure	46	0.41[a] (0.27–0.62)
	Low exposure	59	0.69[a] (0.48–0.99)
Sallmen et al., 1998	Male workers in Finland	282[b]	
	Low or intermediate exposure	80[c]	0.74 (0.51–1.06)
	High or frequent exposure	141[c]	0.80 (0.57–1.11)
Ethylene glycol ethers, work in semiconductor manufacturing			
Samuels et al., 1995	Male semiconductor workers	688[b]	
	Fabrication	118[d]	0.98 (0.80–1.19)
	Masking	23[d]	1.03 (0.70–1.51)
Eskenazi et al., 1995a	Female semiconductor workers		
	Fabrication	19	0.69 (0.38–1.25)
	Exposure to ethylene glycol ethers	3	0.37 (0.11–1.19)

[a]IDR.
[b]Number of couples participating. Paternal exposure was reported.
[c]Number of men reporting exposure to solvents during pregnancies of their spouses.
[d]Number of births.

PREGNANCY

A number of adverse outcomes of pregnancy have been studied for possible associations with exposure to insecticides or solvents. Many of the studies have focused on the risk of fetal loss prior to normal gestation of 40 weeks. Spontaneous abortion (miscarriage) refers to the loss of a fetus prior to 20 weeks of development; after 20 weeks gestation, fetal loss is termed a stillbirth. A birth at less than 37 weeks is referred to as a preterm delivery or premature birth. The overall incidence of spontaneous abortion is estimated to be as high as 43%, with the majority occurring in the 14 days after conception when most pregnancies would not have been detected (Bennett, 1992; Smith and Suess, 1998). About 10% of clinically recognized pregnancies end in spontaneous abortion, usually between 7 and 12 weeks of gestation (NLM, 2002). Completeness of ascertainment is thus a great challenge in epidemiology studies of spontaneous abortion.

The most common identified cause of spontaneous abortion is a genetic abnormality of the embryo. Risk factors for spontaneous abortion include age, maternal illness, cigarette smoking, alcohol use, taking of medications, and having a previous spontaneous abortion. The risk of pregnancy loss is known to increase with increasing maternal age, especially after the age of 30 or 35, and is also high for women under the age of 18. In women who have had one previous spontaneous abortion, the probability of a second is estimated to be 13–26%, and the probability of another increases with successive spontaneous abortions (Smith and Suess, 1998). Several maternal occupational exposures have been associated with the risk of spontaneous

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abortion, including exposure to ethylene oxide, antineoplastic agents, and possibly anesthetic gases.

The committee sought information on whether exposure to insecticides or solvents could result in adverse effects on pregnancies that were conceived after cessation of exposure, but there is a paucity of data on that issue. Several studies provided some information on preconception exposures (generally in the 3 months before conception) and the outcomes of those pregnancies. Most studies, however, examined the results of exposure during pregnancy.

Epidemiologic Studies of Pregnancy Outcomes and Exposure to Insecticides

Maternal Exposure

A nested case–control study by Thomas and colleagues (1992) examined malathion spraying in the San Francisco Bay area to control a Mediterranean fruit fly infestation. The study evaluated spontaneous abortion (n = 559) or stillbirth (n = 37), using 1000 normal live births as the referent group. An exposure index was developed incorporating residential proximity to "spray corridors" and the number and dates of malathion applications. The relative risks of spontaneous abortion ranged from 0.99 to 1.20 for direct exposure to malathion during various periods of gestation. For stillbirth, the strongest association was observed for exposures occurring 1 month before the stillbirth (relative risk [RR] = 1.95, 95% CI = 0.88–4.35). Analysis of intrauterine growth did not show an association between malathion exposure and low birth weight. The investigators noted that exposure misclassification would most likely be nondifferential, thus biasing estimated associations toward the null.

Willis and colleagues (1993) examined a cohort of 535 women enrolled in a perinatal program during 1987–1989 in San Diego County, California, a heavy agricultural-production area where carbaryl and lindane were among the pesticides applied. Maternal interviews were prospective, once during each trimester of pregnancy, and plasma cholinesterase activity was measured at each point. Spontaneous abortion or preterm delivery occurred only in the unexposed group, and there was also a greater incidence of low-birthweight infants in the unexposed population. Those results are difficult to interpret, however, because the number of exposed women in the cohort was not presented. The authors did not report on the correlation between maternal reports of insecticide exposure and plasma cholinesterase activity. The investigators discussed the study's limitations, including the likelihood of exposure misclassification, inability to control for important confounders, and differing degrees of followup among the study participants.

Bell and colleagues (2001a) examined the association between residential proximity to areas of pesticide application and risk of fetal death. They compared the possible maternal exposure for 319 cases (explicitly not due to congenital malformations) with that of the mothers of 611 live births during the same period. They did not find statistically precise elevations regarding this outcome and potential exposure to carbamates, pyrethroids, or phosphates in analyses for each of the three trimesters of gestation.

In 10 agricultural counties of California, Bell and colleagues (2001b) evaluated the relationship between maternal residential proximity to agricultural pesticide applications and the risk of fetal death due to congenital anomalies. They compared the gestational exposure of the mothers of 73 such cases and of 611 live normal births. When several critical periods for exposure during gestation were compared, the largest risks were seen for exposure during the 3rd to 8th week of pregnancy for each of five types of pesticide considered (carbamates, phosphates,

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pyrethroids, halogenated hydrocarbons, and endocrine disruptors). Interestingly, for each of these pesticide types the risks increased when the application area defining exposure was made more specific to a mother's residence (reduced from a 9- to a 1-square-mile area around her home). A followup note (Bell et al., 2001c) presented results from a reanalysis of corrected pyrethroid exposure data, which demonstrated an even more pronounced increase in risk of fetal death following exposure during this high-risk period to that type of pesticide (OR = 3.8, 95% CI = 1.6–9.1 for the 9-square-mile exposure definition); with the revised data there were insufficient cases to perform the 1-square-mile analysis. The 1-square-mile ORs were 2.3 (95% CI = 0.9–6.4) for carbamates and 3.0 (95% CI = 1.4–6.5) for phosphates. As for the previous study (Bell et al. 2001a), the analyses were exclusively restricted to gestation exposures, so the results do not illuminate the consequences of preconceptional exposure.

When maternal occupational exposure to pesticides in general was examined by using job title or recall of exposure, employment in agriculture-related jobs appeared to be related to spontaneous abortion or stillbirth (Goulet and Theriault, 1991; Pastore et al., 1997; Restrepo et al., 1990), but not consistently so (Heidam, 1984; Roan et al., 1984). An ecologic study conducted in 1971–1981 in New Brunswick supported an association with stillbirth, although the exposure was during the second trimester of pregnancy (White et al., 1988). There was little evidence of an association with perinatal death (Kristensen et al., 1997a; Zhang et al., 1992), but an ecologic study in Sudan (Taha and Gray, 1993) did suggest an association.

Paternal Exposure

The relationship between paternal insecticide exposure and pregnancy outcome was examined in a small study of the wives of 32 pesticide applicators in Rome (Petrelli et al., 2000). Lindane and carbamates were among the commonly applied pesticides. The occurrence of spontaneous abortion was compared with that in 51 spouses of food retailers in 1970–1995. The study showed an increased risk of spontaneous abortion among the wives of pesticide applicators (OR = 3.8, 95% CI = 1.2–12.0), but was severely limited by lack of details on selection and recruitment of study subjects, and crude exposure measurement.

Data from the Ontario Farm Family Health Study were used in two epidemiologic studies regarding pregnancy outcomes. The study by Savitz and colleagues (1997) focused on paternal insecticide exposure and pregnancy outcome. Detailed questionnaires regarding pregnancy outcomes and exposures were mailed to eligible farm couples, and telephone interviews were sought for those who did not respond by mail. Investigators examined 3984 pregnancies among 1898 farm couples who participated in the study. The men were interviewed to obtain extensive information on their farming activities over the preceding 5 years, with exposure defined as the mixing or applying of insecticides, pesticides, or fungicides in the 3-month window before conception. Men who had not engaged in farm activities or who reported no chemical exposures during that interval served as the referent group. There were approximately two-fold increases in the risk of spontaneous abortion for couples in which the man reported simultaneous application of carbaryl with herbicides or with insecticides or fungicides (OR = 1.9, 95% CI = 1.1–3.1 and OR = 2.1, 95% CI = 1.1–4.1, respectively). Use of organophosphates on the farm did not result in an increased risk (adjusted OR = 0.9, 95% CI = 0.3–2.4). The risks of small-for-gestational-age deliveries or for preterm births were not increased in workers exposed to any of the specific insecticides or groups of insecticides. The investigators also determined that there was no association between any of the chemical exposures and altered sex ratios (proportion of male births) in this cohort, although a reduced proportion of male births was seen for the fathers who

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did not wear protective gear when applying crop insecticides or fungicides (OR = 0.8). The study did not consider the influence of maternal exposure. Moreover, inclusion of multiple pregnancies per couple might be expected to overstate the significance by inflating the number of events treated as independent, but additional analyses indicated only a modest effect on confidence intervals. The authors state that the lengthy time (often as much as 10–15 years) between pregnancy and recall of chemical exposures may have an effect on the quality of the exposure information.

Parental Exposure

A companion study using data from the Ontario Farm Family Health Study assessed the couple as the unit of analysis in examining the relationship between specific groups of pesticides and spontaneous abortion (Arbuckle et al., 2001). Again, multiple pregnancies per couple were included; 2110 women reported 3936 pregnancies, 395 of which ended in spontaneous abortion. The spontaneous abortions were dichotomized into early (less than 12 weeks of gestation) and late (12–19 weeks). Exposure information was obtained from both husband and wife, and pesticides were divided into four major classes: insecticides, herbicides, fungicides, and "other." Exposures were examined during preconception (3 months before and the calendar month of conception) and postconception (the 3 months corresponding to the first trimester). Neither carbaryl, organophosphates, nor insecticides in general were related to overall, early, or late spontaneous abortion. The analysis of preconception exposure to carbaryl found an OR of 1.2 for spontaneous abortion (95% CI = 0.9–1.7, 41 exposed cases). Postconception exposures, however, were associated with a slight decrease in the occurrence of spontaneous abortion (OR = 0.8, 95% CI = 0.5–1.2, 21 exposed cases). Consideration of the couple as the unit of exposure improved the analysis over that of only paternal exposures in the same cohort (Savitz et al., 1997).

A study using the National Natality and Fetal Mortality Surveys, which included both maternal and paternal recall of exposure to "pesticides, herbicides, and fungicides," reported an association of maternal and paternal exposure with stillbirth, but not with preterm delivery (Savitz et al., 1989a). The nonspecific nature of the exposure measurements makes it difficult to use the results of this study in weighing the evidence of an association between insecticides and pregnancy outcomes.

Summary and Conclusion

The body of literature on insecticide exposure and pregnancy outcomes during the preconception period is limited mainly by the nonspecific nature of the exposure assessments. Among studies that describe an ecologic measure of exposure to the insecticides under review, the evidence of an association with spontaneous abortion or stillbirth is weak. Two studies examined the same cohort of farm couples and found some evidence of a relationship between exposure to carbaryl and spontaneous abortion; however, their usefulness is limited by the length of time between when the events of interest occurred and when the information was gathered for the study.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to the insecticides under review and spontaneous abortion or other adverse pregnancy outcomes.

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Epidemiologic Studies of Pregnancy Outcomes and Exposure to Organic Solvents

Maternal Exposure

The possible association between maternal solvent exposure and adverse pregnancy outcomes have been investigated in studies in a number of industries, including dry cleaning, semiconductor and electronics manufacturing, and pharmaceutical and petrochemical research. Most of the studies have focused on the effects of occupational exposure during pregnancy. Studies that asked women about their occupational histories were generally not designed to separate potential effects of exposure during pregnancy from the effects of exposure before pregnancy.

A number of epidemiologic studies have examined pregnancy and birth outcomes among female semiconductor workers exposed to ethylene glycol ethers (particularly in the fabrication process) and other chemicals. However, no studies were identified that focused on preconception exposure of the mother and birth outcomes. A set of retrospective cohort studies in the semiconductor industry examined spontaneous abortion among fabrication and nonfabrication workers (Beaumont et al., 1995) and analyzed exposure to specific agents in this cohort (Swan et al., 1995). A prospective cohort study in the industry (Eskenazi et al., 1995b) monitored spontaneous abortion and early fetal loss as detected by urinary human chorionic gonadotropin. A later study found positive associations between high potential exposure to ethylene glycol ethers and spontaneous abortion in female employees in two semiconductor manufacturing plants with an indication of a trend of increased risk of spontaneous abortion with higher potential exposure (Correa et al., 1996). Several other studies of workers in the semiconductor or electronics manufacturing industries have produced inconsistent results. The earliest study by Pastides and colleagues (1988) found an elevated increase in spontaneous abortion among women working in the photolithography process in the industry, in which exposure to solvents was likely (RR = 1.75, 95% CI = 0.77–3.25). No association between semiconductor fabrication and spontaneous abortion was reported by Shusterman and colleagues (1993), but the number of pregnancies in women exposed to semiconductor chemicals was small (n = 15). Another study of a small number of spontaneous abortions included extensive exposure-assessment efforts in the British semiconductor industry; the number of cases was too small for a detailed analysis of specific exposures (Elliott et al., 1999).

Several studies have investigated the effects on pregnancy of employment in the dry-cleaning industry (a likely source of occupational exposure to solvents). Kyyronen and colleagues (1989) conducted a case–control study of spontaneous abortion and congenital malformations in dry-cleaning and laundry workers in Finland and reported an increased risk in those with “high” exposure.

Olsen and colleagues (1990) studied low birthweight, congenital malformations, and spontaneous abortion among dry-cleaning and laundry workers in Sweden, Norway, Denmark, and Finland, by linking company records to their corresponding national medical and hospital records. When the data from Sweden, Denmark, and Finland were combined, a slight increase in the risk of spontaneous abortion was seen for women with potential low exposure, defined as work in a dry-cleaning facility but not engaging in work known to produce high exposure (OR = 1.17, 95% CI = 0.74–1.85); the increase was more marked for women in jobs with potential high exposure, defined as performing dry-cleaning work or spot removal for at least one hour per workday (OR = 2.88, 95% CI = 0.98–8.44).

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In the United Kingdom, Doyle and colleagues (1997) compared a cohort of dry-cleaning workers potentially exposed to tetrachloroethylene to laundry workers. They found a small increase in the risk of spontaneous abortion (OR = 1.03, 95% CI = 0.48–2.21), when analysis was restricted to first pregnancies and adjusted for maternal age and year of birth.

Using a combined-outcome measure (spontaneous abortion, perinatal death, congenital malformations, and low birthweight), Ahlborg (1990) studied two cohorts of women working in laundry or dry-cleaning facilities in Sweden. He found an elevated but imprecise estimate of risk adverse pregnancy outcome associated with exposure to tetrachloroethylene during the first trimester.

Lindbohm and colleagues (1990) conducted a study of Finnish women occupationally exposed to organic solvents. Each woman's level of exposure was categorized based on occupation, work description, self-reports of solvent exposure, and biologically monitored data when available. Five percent of the workers had their exposure to solvents biologically monitored during the first trimester of their pregnancy. After adjusting for potential confounders, they found an association between solvent exposure and spontaneous abortion (OR = 2.2, 95% CI = 1.2–4.1). The odds ratios increased with the magnitude of exposure to aliphatic hydrocarbons as a group or to trichloroethylene specifically.

Windham and colleagues (1991) conducted a case–control study of spontaneous abortions in California. Exposure to solvents was ascertained by telephone interview. Among women who were employed (n = 1361) there was a slightly increased risk of spontaneous abortion associated with exposure to solvents. There was an increased risk of spontaneous abortion in women exposed to aliphatic solvents specifically (OR = 1.8, 95% CI = 1.1–3.0), but no trend of increasing risk with higher exposure. The study also looked at fetal-growth measures, but did not find associations between solvent exposure and intrauterine growth retardation.

A case–control study in the shoe industry (Agnesi et al., 1997) used crudely defined exposure categories. The authors reported an association between "high" solvent exposure and spontaneous abortion (OR = 3.85, 95% CI = 1.24–11.9), adjusting for coffee consumption and previous spontaneous abortion. A retrospective cohort study in the petrochemical industry in China (Xu et al., 1998) reported an association between benzene and spontaneous abortion (RR = 2.5, 95% CI = 1.7–3.7).

Taskinen and colleagues (1994) conducted a case–control study of female laboratory workers potentially exposed to solvents and spontaneous abortion (206 cases and 329 controls). They reported increased risks with exposure to toluene (OR = 4.7, 95% CI = 1.4–15.9) and xylene (OR = 3.1, 95% CI = 1.3–7.5). Another study by the same authors of women working in pharmaceutical factories found an association between exposure to methylene chloride and spontaneous abortion (OR = 2.3, p = 0.06) (Taskinen et al., 1986).

Lipscomb and colleagues (1991) examined maternal occupational solvent exposure among the residents of Santa Clara County, California, an area where possible effects of contaminated drinking water on pregnancy outcomes had been of concern. An increased risk of spontaneous abortion was associated with first-trimester solvent exposure (OR = 3.34, 95% CI = 1.42–7.81) when confounders, including previous miscarriage, were controlled for in the analysis.

In a study of maternal occupational exposure to a number of chemicals, Seidler and colleagues (1999) reported a slightly increased risk for associations between exposure to solvents and small-for-gestational-age infants.

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Paternal Exposure

A study in Finland used a nationwide database of pregnancy outcomes, data from clinics and hospitals, and census data to examine the effect of paternal occupational exposure to solvents and other chemicals on the occurrence of spontaneous abortion (Lindbohm et al., 1991). A job–exposure matrix based on occupation and industry was used to classify exposures. The study used the time of spermatogenesis (80 days before conception) as the relevant time for exposure. Increased risks of spontaneous abortion were associated with exposure to solvents used in petroleum refineries (OR = 2.2, 95% CI = 1.3–3.8) and solvents used in the manufacture of rubber products (OR = 1.9, 95% CI = 1.2–2.8). Examination of the relationship between spontaneous abortion and exposure to specific solvents or to solvents used in other manufacturing processes, however, found mixed results (imprecise ORs ranging from 0.3 to 1.5). The study did not rely on recall of exposure and thus had less bias than many other studies of spontaneous abortion, but it did not control for other occupational exposures and so left open the possibility of confounding by other hazards in these industries.

Another study in Finland examined spontaneous abortion and congenital malformations for a group of 120 male workers, many of whom had been biologically monitored for organic-solvent exposure by the Finnish Institute of Occupational Health (Taskinen et al., 1989). Information on spontaneous abortion was obtained from the Hospital Discharge Register. Three controls were identified for each case, matching to the mother's age within 30 months. Questionnaires sent to both partners asked the man to record his occupational and medical history and frequency of solvent exposure during the year of conception, and asked the woman to provide information on her occupational and lifestyle exposures in the first trimester of the pregnancy. Exposure was defined as high or frequent if the worker had biological monitoring measurements above the general population levels or had handled solvents daily. The study controlled for a number of potential confounders, including maternal heavy lifting, history of previous spontaneous abortion, exposure to other organic solvents and dusts, and maternal exposure to solvents. Consistent increases in risk were seen in association with high or frequent paternal exposure to toluene (OR = 2.3, 95% CI = 1.1–4.7), high or frequent use of organic solvents (OR = 2.6, 95% CI = 1.2–5.9), and high or frequent use of miscellaneous organic solvents (OR = 2.1, 95% CI = 1.1–3.9). The analysis did not, however, find any noteworthy dose–responses for paternal exposure to solvents or categories of solvents. An analysis by paternal occupation found associations with employment as a painter (OR = 3.3, 95% CI = 1.6–6.8) or woodworker (OR = 3.8, 95% CI = 1.2–11.9).

The effect of paternal exposure to benzene on the risk of spontaneous abortion was examined in a study of male workers at two chemical plants in France (Stucker et al., 1994). Occupational histories were provided by the companies and were categorized according to benzene exposure (none; low, <5 ppm; and moderate, ≥5 ppm). Wives of 823 male workers filled in a questionnaire regarding their pregnancies. The study did not find pronounced increases in the incidence of spontaneous abortion when the fathers were exposed to benzene during the 3 months before conception (RR = 1.1, 95% CI = 0.6–2.0) or when all past exposures to benzene were considered (RR = 1.3, 95% CI = 0.9–2.0).

A small study found approximately equivalent rates of spontaneous abortion between the wives of 17 dry-cleaning workers (11.1%) and the wives of 32 laundry workers (15.2%) (Eskenazi et al., 1991).

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Parental Exposure

Several studies have examined potential associations between maternal and paternal exposure to solvents and pregnancy outcomes other than spontaneous abortion, including low birthweight and stillbirth. The results have been inconsistent. Ahlborg and colleagues (1989) reported that solvent exposure was not associated with any late-pregnancy outcomes. In a prospective study, Chen and colleagues (2000) found an association between low birthweight and benzene exposure, which was intensified when benzene was combined with work stress.

Goulet and Theriault (1991) conducted a study of stillbirth (n = 227) that included detailed exposure assessment. They reported no association between stillbirth and solvent exposure.

A study of parental occupational exposure reported a weak association between paternal solvent exposure and small-for-gestational-age infants (Savitz et al., 1989b).

Summary and Conclusion

Only a few studies have examined the potential for an association between preconception exposure to solvents among males and spontaneous abortion, and their results have been inconsistent (Table 8.4). Although there were many studies of the effects of maternal solvent exposure during pregnancy, no studies were found that specifically assessed preconception exposure among females and spontaneous abortion. The question of the potential for persistent effects of solvent exposure (after cessation of that exposure) on subsequent pregnancies has not been adequately examined. The body of evidence on other pregnancy outcomes (such as small-for-gestational-age infants and stillbirth) is also inconsistent.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to specific organic solvents under review or solvent mixtures and spontaneous abortion or other adverse pregnancy outcomes.

TABLE 8.4 Selected Epidemiologic Studies: Spontaneous Abortion and Paternal Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Lindbohm et al., 1991	Men in Finland		
	Solvents, petroleum refineries	16	2.2 (1.3–3.8)
	Solvents, manufacture of rubber products	26	1.9 (1.2–2.8)
	1,1,1-Trichloroethane	3	1.5 (0.4–5.0)
	Benzene (low level exposure)	55	1.0 (0.7–1.3)
	Trichloroethylene	5	0.9 (0.3–2.1)
	Tetrachloroethylene	3	0.7 (0.2–2.4)
Taskinen et al., 1989	Men in Finland		
	Organic solvents		
	Low or rare exposure	14	2.8 (1.0–7.9)
	Intermediate exposure	17	1.8 (0.7–4.6)
	High or frequent exposure	72	2.6 (1.2–5.9)
	Toluene		
	Low or rare exposure	11	0.9 (0.4–2.2)
	Intermediate exposure	9	0.7 (0.3–1.7)
	High or frequent exposure	28	2.3 (1.1–4.7)

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Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
	Xylene—high or frequent exposure	19	1.6 (0.8–3.2)
	Halogenated hydrocarbons		
	Low or rare exposure	14	1.1 (0.5–2.6)
	High or frequent exposure	6	0.8 (0.3–2.2)
Stucker et al., 1994	Male workers at chemical plants exposed to benzene		
	Exposed to benzene during the 3 months before conception	NA	1.1 (0.6–2.0)
	Any past exposure to benzene	NA	1.3 (0.9–2.0)

NOTE: NA = not available.

CONGENITAL MALFORMATIONS

Congenital malformations involve major or minor abnormalities of structure or function that are present at birth. Major congenital malformations are seen in about 2–3% of newborns (Holmes, 1999); some anomalies and developmental defects (such as aneuploidy and mental retardation) can go undetected until after the first year of life. As infant mortality has declined in the United States, the proportion of infant deaths attributable to birth defects has increased. Birth defects are now the leading cause of death in infants in the United States and accounted for 19.6% of the 27,937 infant deaths in 1999 (Hoyert et al., 2001).

The etiology of many congenital malformations is yet to be discovered (Holmes, 1999). About 25% of congenital malformations have primarily genetic causes (including chromosomal abnormalities and single gene mutations); but most involve varying combinations of genetic and environmental factors. Uterine factors (such as crowding, breech presentation, and vascular disruption) are involved in a small percentage of cases. Other risk factors are maternal infections (such as rubella and syphilis), maternal diabetes, high maternal age (associated with Down syndrome), and folate deficiency (associated with neural tube defect). An estimated 3% of congenital malformations are caused by teratogenic exposures, but even in the case of well-known teratogens (such as thalidomide, diethylstilbestrol, androgenic hormones, coumarin anticoagulants, lithium, and tetracycline) manifestation is influenced by the genetic constitution of the mother and fetus.

The evaluation of the etiology of specific congenital malformations is difficult because of the rarity of each type; for example, the prevalence of spina bifida is generally reported to be 4.6 cases per 10,000 births (Lary and Edmonds, 1996). Anomalies are often grouped with the intention of increasing the study's power to detect potential associations with suspected exposure, but that approach can compromise power rather than enhance it. It is increasingly apparent that specific congenital malformations can differ in their etiology, and the circumstances of an exposure (such as timing and route) can differ between anomalies (Selevan et al., 2000). Other methodologic issues include the fact that there are few suspected or known risk factors to take into account when adjusting for potential confounders. Further, analysis can be complicated by multiple pregnancies (and multiple fetuses per pregnancy), which cannot be considered independent events. Since only embryos and fetuses that survive are included in an analysis, it may be difficult to detect an association with malformations for an agent that also decreases survival.

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Epidemiologic Studies of Congenital Malformations and Exposure to Insecticides

Neural-Tube Defects and Other Central Nervous System Anomalies

A neural-tube defect (NTD) occurs early in gestation (prior to the 28th day) and involves damage to the tissue that will become the brain or spinal cord. Spina bifida (involving protrusion of the spinal cord) and anencephaly (involving the absence of parts of the skull or the cerebral hemispheres of the brain) comprise the majority of NTDs. Due to the developmental stage when they occur, exposures occurring at the beginning of gestation or exposure to compounds with long half-lives are potentially relevant to studies of NTDs.

Shaw and colleagues (1999a) compared maternal pesticide exposure in cases of selected congenital anomalies (662 orofacial clefts, 207 conotruncal defects, 165 limb defects, and 265 NTDs) ascertained by the California Birth Defects Monitoring Program and 734 randomly selected controls born in the same geographic area and period (1987–1989). The mothers were interviewed about exposure to pesticides from several sources for the period from 1 month before to 3 months after conception. In general, the women were unable to identify the specific pesticide chemicals to which they were exposed. Positive associations with NTDs were reported for professionally applied pesticides in the home (OR = 1.6, 95% CI = 1.1–2.5), but a weaker association was found when the mother applied pesticides in the home (OR = 1.1, 95% CI = 0.8–1.7). A slightly elevated risk was seen with the use of insect foggers (OR = 1.1, 95% CI = 0.6–2.0), but positive associations were not seen between NTDs and maternal use of insect repellent or use of flea collars on pets. The ORs for NTDs in the children of mothers categorized as "maybe" and "likely" exposed to pesticides occupationally were 1.3 (95% CI = 0.6–2.7) and 0.9 (95% CI = 0.2–3.8), respectively. The study examined several congenital anomalies and multiple sources of exposure, but the exposure measures were nonspecific with regard to particular insecticides. The study did not independently assess preconception exposures.

In anther study, Shaw and colleagues (1999b) focused solely on NTDs and maternal exposure to occupation- and hobby-related chemicals, including several classes of insecticides. Cases were ascertained through review of medical records of infants and fetuses in whom NTDs were diagnosed in California from June 1989 to May 1991. Control infants were randomly selected from a population-based cohort of California births during the same period. For 538 cases and 539 controls, mothers were interviewed to obtain detailed work histories and information on specific hobbies, including gardening. The primary period of interest was from 3 months before conception through the first trimester of pregnancy (periconception). An industrial hygienist, blinded to case–control status, classified the women as likely to have been, maybe, or not exposed to 74 chemical-agent groups. Potential association with NTDs was evaluated for periconceptional maternal exposure to 48 chemical groups. The authors reported elevations in risk associated with exposure to carbamate insecticides (OR = 1.2, 95% CI = 0.38–3.7) or to organophosphates (OR = 1.2, 95% CI = 0.60–2.5). When the insecticides were grouped, the risk of NTDs increased (OR = 1.3, 95% CI = 0.81–2.1). Analyses comparing the 3-month preconception period with the 3-month postconception period suggested the effect might be somewhat greater for exposure during the postconception period (carbamates: preconception OR = 1.5, 95% CI = 0.41–5.1; postconception OR = 2.1, 95% CI = 0.51–7.6 and organophosphates: preconception OR = 1.2, 95% CI = 0.56–2.5; postconception OR = 1.6, 95% CI = 0.71–3.7). The period between the birth (or NTD diagnosis) and the maternal interview was not stated, and recall bias was possible. Exposure misclassification remains a possibility, but is likely to be nondifferential, thus biasing associations toward the null. Adjustment for

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maternal education, race or ethnicity, and multivitamin use did not produce substantially different results.

Other studies have used broad exposure categories without specific measures of insecticide use. A case–control study in Finland reported an adjusted OR of 1.2 (95% CI = 0.6–2.4) between maternal agricultural work and CNS defects (Nurminen et al., 1995). Blatter and colleagues (1997) reported on a multicenter study in the Netherlands that found an OR for spina bifida of 1.7 (95% CI = 0.7–4.0) for moderate or high paternal exposure to pesticides. The level of exposure was categorized by the investigators based on interview responses regarding the nature of the exposures, exposure frequency, and use of protective equipment. A study of births to licensed pesticide applicators in Minnesota found six cases of CNS anomalies compared with 242 in the general population (age-adjusted OR = 1.10, 95% CI = 0.50–2.40) (Garry et al., 1996). The focus of the study was chlorophenoxy herbicide and fungicide use. Kristensen and colleagues (1997b) conducted a study of birth defects reported to the Medical Birth Registry of Norway and pesticide use in farmers and found an adjusted OR for CNS defects of 2.30 (95% CI = 1.31–4.04). As noted, the major limitation of those studies for the purposes of this review was the characterization of pesticide exposure without an analysis of specific types of pesticides.

Congenital Heart Malformations

Loffredo and colleagues (2001) conducted a case–control study of congenital heart defects, including transposition of the great arteries (TGA), as part of the Baltimore–Washington Infant Study. Maternal pesticide exposure for 180 cases (including 66 cases of TGA) born in 1987–1989 was compared with 771 randomly selected infants born in the same period. The critical exposure period was the first trimester of pregnancy and the preceding 3 months. Questions were asked about a wide range of potential confounders, including family history of heart defects, cigarette smoking, alcohol drinking, and socioeconomic status. For the 21 TGA cases and 179 controls with insecticide exposure during the critical period, the study found an increased OR of 1.5 (95% CI = 0.9–2.6), with similar results for insecticide exposure in the 4–6 months before pregnancy (OR = 1.6, 95% CI = 0.9–2.9). This study was population-based, and pediatric cardiologists confirmed all diagnoses. The authors tried to reduce exposure misclassification by conducting interviews within a year after the birth of the infants. The authors stated that there might have been confounding by factors related to socioeconomic status, such as poor housing. There could also have been confounding by exposure to other pesticides—rodenticides and herbicides—that showed stronger associations.

The study by Shaw and colleagues (1999a) described above examined conotruncal heart defects and maternal pesticide exposure during the period from 1 month before to 3 months after conception. The study found positive associations with several categories of exposure, including maternal application of pesticides during gardening (OR = 3.1, 95% CI = 1.3–7.3), use of insect repellent (OR = 2.2, 95% CI = 1.3–3.9), and use of more than one pet-flea product (OR = 1.2, 95% CI = 0.8–1.8). Positive associations were not found with use of insect foggers or use of pet-flea collars.

Other studies of cardiac anomalies have information only on the broader category of pesticides. In a related publication of the Baltimore–Washington Infant Study, Wilson and colleagues (1998) reported an attributable fraction[2] of 5.5% (95% CI = 0.8–10.1%) for maternal or paternal periconception pesticide exposure and a specific congenital heart defect,

[2]Attributable fraction is the fraction of cases in the population that might have been prevented if the risk factor had been absent.

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isolated/simplex membranous ventricular septal defect. In a study comparing exposure of the mothers of children with Down syndrome, Fixler and Threlkeld (1998) found an OR of 0.79 (95% CI = 0.44–1.44) for children's congenital heart defects and maternal prenatal exposure to pesticides.

Multiple and Other Malformations

Thomas and colleagues (1992) reported a nested case–control study of reproductive outcomes and potential exposure to malathion during pregnancy; the exposure resulted from spraying to control a Mediterranean fruit fly infestation in the San Francisco Bay area. The investigators found a slightly increased risk for reportable anomalies in offspring of women who resided in an active spraying corridor during their first trimester (adjusted RR = 1.20, 95% CI = 0.83–1.73). Limb (n = 38) and orofacial (n = 8) anomalies were positively associated with potential malathion exposure in the first trimester (adjusted RR = 1.73, 95% CI = 0.87–3.46 and adjusted RR = 3.35, 95% CI = 0.61–18.5, respectively).

Grether and colleagues (1987) conducted a study of exposure during 1981–1982 to aerially applied malathion, in the same counties as Thomas and colleagues (1992). For 1981, they found strong positive associations for anomalies of the ear, bowing of the long bones of the leg, varus deformities, grouped clubfoot diagnoses, and tracheoesophageal fistula. In 1982, however, the incidences of all these anomalies were not associated with malathion spraying.

Schwartz and LoGerfo (1988) employed county pesticide-use data to estimated exposure in a study of limb reduction defects. Comparing maternal residence in California counties with high versus minimal pesticide use, they found an OR of 1.9 (95% CI = 1.2–3.1).

Garcia and colleagues (1998) reported a case–referent study of 261 matched pairs of infants in eight hospitals in agricultural areas of Spain and paternal pesticide exposure. Following interviews with the fathers, 28 chemical classes of pesticides and 78 active ingredients were identified as having been used during the period from 3 months before conception through the first trimester of pregnancy. After control for common confounders, there was no evidence of increased risk of congenital anomalies posed by OP or carbamate use. Malathion use also did not increase the risk of congenital anomalies (OR = 0.30, 95% CI = 0.06–1.43). A limitation of the study was that congenital anomalies were treated as a group rather than as specific defects, which would tend to bias associations toward the null.

Paternal exposure to pesticides was also examined by Lin and colleagues (1994) in a study of limb reduction defects. Cases were identified from the New York State Congenital Malformation Register, and birth-certificate data were used to provide demographic and occupational information on the parents. Pesticide- and insecticide-exposure information was determined from place of residence and type of occupation. Limb reduction defects were not found to be associated with paternal or maternal exposure to insecticides (OR = 1.0, 95% CI = 0.5–1.7 and OR = 0.7, 95% CI = 0.4–1.5, respectively).

Summary and Conclusion

Although there have been numerous studies on the relationship between congenital malformations and various sources of parental pesticide exposure, few have looked at the relationship between congenital malformations and insecticides, particularly the specific insecticides examined in this report (Table 8.5). Various approaches were used to estimate exposures, ranging from self-reports to linkages with aerial spraying records. The rarity of the malformations means the numbers of exposed cases is limited, and so constrains the studies'

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power to detect actual effects. The few studies that examined maternal or paternal preconception exposures did not find clear and consistent evidence of an association with any type of malformation.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to the insecticides under review and congenital malformations.

TABLE 8.5 Selected Epidemiologic Studies: Congenital Malformations and Exposure to Insecticides

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Maternal Exposure			
NTDs and CNS Anomalies			
Shaw et al., 1999a	Maternal exposure 1 month before to 3 months after conception		
	Use of insect foggers	20	1.1 (0.6–2.0)
	Professionally applied pesticides in the home	53	1.6 (1.1–2.5)
	Mothers applying pesticides in the home	54	1.1 (0.8–1.7)
	Insect-repellent use	16	1.0 (0.6–1.9)
	Maternal occupational exposure likely	3	0.9 (0.2–3.8)
Shaw et al., 1999b	Occupational and hobby-related exposures 3 months before conception through pregnancy		
	Carbamates	6	1.2 (0.38–3.7)
	Organophosphates	17	1.2 (0.60–2.5)
	Pyrethrins	7	1.0 (0.36–2.8)
	Insecticides	40	1.3 (0.81–2.1)
Heart Malformations			
Loffredo et al., 2001	Maternal exposure and infants born with transposition of the great arteries		
	Insecticides—critical period	32	1.5 (0.9–2.6)
	Insecticides—4–6 months before pregnancy	28	1.6 (0.9–2.9)
Shaw et al., 1999b	Maternal exposure 1 month before to 3 months after conception		
	Mothers applying pesticides during gardening	12	3.1 (1.3–7.3)
	Insect-repellent use	25	2.2 (1.3–3.9)
	More than one pet-flea collar product used	53	1.2 (0.8–1.8)
	Insect-fogger use	12	0.8 (0.4–1.7)
Paternal Exposure			
Multiple or Other Malformations			
Garcia et al., 1998	Paternal exposure for infants born in agricultural areas of Spain		
	Malathion	6	0.30 (0.06–1.43)
	Carbamates	10	0.81 (0.30–2.22)
	Organophosphates	31	0.77 (0.38–1.58)
Lin et al., 1994	Parental exposure for infants born with limb reduction defects in New York state		
	Paternal exposure to insecticides	23	1.0 (0.5–1.7)
	Maternal exposure to insecticides	13	0.7 (0.4–1.5)

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Epidemiologic Studies of Congenital Malformations and Exposure to Organic Solvents

Neural Tube Defects and Other Central Nervous System Anomalies

A study by Holmberg and colleagues used the Finnish Register of Congenital Malformations to identify children with CNS anomalies (Holmberg, 1979; Holmberg and Nurminen, 1980). They reported that maternal occupational exposure to solvents was associated with an increased incidence of anomalies.

Shaw and colleagues (1999b) studied occupational and hobby-related exposures of mothers of 538 children with NTDs (diagnosed June 1989–May 1991) and 539 controls born in selected California counties. Maternal interviews assessed exposures from 3 months before to 3 months after conception (periconception) and included a detailed work history and questions about hobbies. An industrial hygienist used the data to create exposure classifications for 74 chemical-agent groups, exposure to 48 of which were assessed for NTDs. In the extensive analysis, periconceptional maternal exposure to glycol ethers and derivatives resulted in an OR of 0.93 (95% CI = 0.66–1.3), with 75 exposed cases. The study found inconsistent results for associations between NTDs and any of the categories of solvent exposure considered, such as aliphatic chlorinated hydrocarbons (OR = 1.1), aliphatic alcohols (OR = 0.87), and ketones (OR = 0.71). The strengths of this study included a detailed exposure assessment that was based on interviews conducted close to the birth and an analysis that controlled for medical risk factors. The study did not provide a separate analysis of data regarding preconception exposure, but provides some insights into exposure–outcome relationships in the 3 months before and after conception.

Two studies by Blatter and colleagues (1996, 1997) examined occupational exposures of mothers and fathers of children born with spina bifida in nine hospitals in the Netherlands. The controls were healthy children born in the same period, selected from several of the hospitals and from the general population. In a two-step data-collection process, questionnaires were mailed to case and control parents to gather information on occupations and potential confounders, followed by personal interviews regarding job- and task-specific information. In the study of maternal exposures (Blatter et al., 1996), the period of interest was from 2 weeks before conception to 6 weeks after conception. Exposures were assessed as none, light, moderate, and heavy. No differences were found in risk of spina bifida with exposure to all organic solvents; the analysis of 29 exposed cases and 35 exposed controls resulted in an OR of 0.9 (95% CI = 0.6–1.6).

In the companion study (Blatter et al., 1997), paternal occupational exposures were assessed for the period from 3 months before conception to 1 month after conception. Interviews were conducted with 122 fathers of children with spina bifida and 411 fathers of controls. The study controlled for a number of medical risk factors, including maternal diabetes and the use of antiepileptic medications. The investigators did not find an increased risk associated with paternal exposure to solvents at any level (OR = 0.7, 95% CI = 0.4–1.1), low solvent exposure (OR = 0.6), or moderate to high solvent exposure (OR = 0.9).

Other studies of paternal exposure and CNS anomalies that were examined by the committee used broad exposure categories based on occupational titles (e.g., Brender and Suarez, 1990; Irgens et al., 2000; Olshan et al., 1991). Thus, they did not have specific information on solvent exposure necessary to inform conclusions.

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Congenital Heart Malformations

As part of the Baltimore–Washington Infant Study, Wilson and colleagues (1998) examined risk factors potentially associated with several major cardiac malformations. They interviewed 1585 parents of children born in 1981–1989 with structural heart defects. The exposure period of interest encompassed the 3 months before and after the mother's last normal menstrual period. The study found attributable fractions of 4.6% (95% CI = 3.2–6.0%) for solvent or degreasing-agent exposure with hypoplastic left heart, 3.0% (95% CI = 1.6–4.5%) for solvent exposure with coarctation of the aorta, and 5.1% (95% CI = 1.2–8.9%) for painting with atrioventricular septal defect in Down syndrome.

Tikkanen and Heinonen published several case–control studies of maternal exposure during early pregnancy and different congenital cardiac malformations. The earliest study found an adjusted RR of 1.3 (95% CI = 0.8–2.2) for maternal solvent exposure during the first trimester and all cardiovascular malformations (Tikkanen and Heinonen, 1988). In a study focused on atrial septal defects in 50 cases compared with 756 controls, maternal first-trimester occupational exposure to solvents resulted in an increased RR of 2.6 (95% CI = 0.7–9.1) (Tikkanen and Heinonen, 1992a). In a similar analysis for conal malformations of the heart, Tikkanen and Heinonen (1992b) found no association with maternal exposure to solvents during the first trimester (OR = 0.6, 95% CI = 0.2–1.4).

Oral Clefts

Holmberg and colleagues (1982) found that more mothers of children with oral clefts had occupational exposure to solvents than did mothers of unaffected children born in the same time period and geographic area.

A case–control study in France compared exposure to solvents by mothers whose children were born from 1985 to 1989 with or without oral cleft (Laumon et al., 1996). Interviews with each mother focused on exposures in the first 2 months after conception. Among all the categories of solvents considered, increased risks were found for exposure specifically to halogenated aliphatic solvents (OR = 4.40, 95% CI = 1.41–16.15) and for exposure to any solvent (OR = 1.62, 95% CI = 1.04–2.52). The estimates of the risk of oral clefts associated with other categories of solvent exposures were not markedly elevated.

Maternal occupational exposures during pregnancy were also the focus of studies by Cordier and colleagues. In a preliminary case–control study in two regions of France, the mothers of 325 children with major malformations and 325 normal referents were interviewed about exposures during pregnancy (Cordier et al., 1992). The study found an increased estimated risk for maternal solvent exposure and children with oral clefts (OR = 7.9, 90% CI 1.8–44.9). A later multicenter case–control study by the same investigators (Cordier et al., 1997) focused on maternal exposure to glycol ethers during the first trimester of pregnancy. The overall OR for congenital malformations was 1.44 (95% CI = 1.10–1.90) after adjustment for several potential confounders. Positive associations were found between first-trimester exposure to glycol ethers and several specific types of congenital malformations considered in the study: NTD (OR = 1.94, 95% CI = 1.16–3.24), spina bifida (OR = 2.37, 95% CI = 1.22–4.62), cleft lip (OR = 2.03, 95% CI = 1.11–3.73), and multiple anomalies (OR = 2.00, 95% CI = 1.24–3.23). The most recent study by those investigators also focused on first-trimester maternal occupational exposure (Lorente et al., 2000). An increased risk was seen for exposure to glycol ethers and cleft lip (with or without cleft palate) on the basis of 23 exposed cases (OR = 2.10,

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95% CI = 1.14–3.88), but the risk for cleft palate alone was not as elevated (OR = 1.82, 95% CI = 0.82–4.03).

Other Types of Congenital Malformations

Potential risk factors for the congenital malformation gastroschisis were examined in a case–control study by Torfs and colleagues (1996). The registry of the California Birth Defects Monitoring Program was used to ascertain 110 cases of infants born with abdominal wall defects, and a pediatric geneticist reviewed the diagnosis. The 220 controls for the study did not have a congenital malformation and were matched on maternal age and ethnicity. Interviews included questions on hobbies during pregnancy, occupational exposures during the 3 months before conception and the first trimester of pregnancy, and medications and illnesses during the first trimester. An industrial hygienist evaluated the type of exposure associated with the occupations and categorized exposures as low or high intensity based on the working conditions, duration of work, and route of exposure. The study found increased risks associated with high solvent exposure (OR = 3.84, 95% CI = 1.61–9.17) on the basis of 15 exposed cases; the risk posed by low exposure was also increased (OR = 2.28, 95% CI = 0.99–5.24). High exposure specifically to aromatic hydrocarbons was associated with abdominal defects (OR = 4.74, 95% CI = 1.45–15.49). This study's outcomes were carefully confirmed, but little other research has been directed at this specific malformation.

McDonald and colleagues (1988) examined occupational risks of congenital malformations in 47,913 pregnancies of women in Montreal and found no evidence of increased risk of congenital malformations associated with solvent exposure in any of the groups.

Khattak and colleagues (1999) reported the results of a prospective study of solvent exposure and congenital malformations in women who were occupationally exposed to solvents. Those women sought counseling (1987–1996) about their exposures at a pregnancy and antenatal counseling service in Toronto. Women who worked with organic solvents during at least their first trimester (n = 125) were compared with women who participated in the counseling service but did not work with solvents or other suspected teratogens. The study found that 13 of the solvent-exposed women had children with major malformations compared with one in the control group (RR = 13.0, 95% CI = 1.8–99.5). The malformations included ventricular septal defect, NTD, and clubfoot. The prospective design reduces the likelihood of differential exposure misclassification and selection bias, because the outcome had not occurred at the time of exposure assessment and subjects had not been recruited retrospectively. In addition, drawing the comparison group (non-solvent exposed women) from the same counseling service as the solvent-exposed women further minimized the possibility of selection bias.

Summary and Conclusion

Few studies of solvent exposure and congenital malformations focused on preconception exposure of either mothers or fathers (Table 8.6). Paternal preconception exposure to solvents was examined in a study that did not find an increased risk of spina bifida in the children (Blatter et al., 1997). A few studies included preconception exposure and gestational exposure but did not provide a separate analysis of exposures before pregnancy; therefore, these studies are unable to present risks independently for the preconception period. A case–control study on gastroschisis found increased risks posed by solvent exposure in the period from preconception through the first trimester (Torfs et al., 1996). A study of NTDs by Shaw and colleagues (1999a) found inconsistent results of periconception exposure to various classes of solvents.

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The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to the specific organic solvents under review or solvent mixtures and congenital malformations.

TABLE 8.6 Selected Epidemiologic Studies: Congenital Malformations and Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Maternal exposure			
Neural tube defects			
Shaw et al., 1999	Occupational and hobby-related exposure (3 months before conception to 3 months after conception)		
	Aliphatic alcohols	143	0.87 (0.67–1.1)
	Aliphatic chlorinated hydrocarbons	26	1.1 (0.62–1.9)
	Glycol ethers and derivatives	75	0.93 (0.66–1.3)
	Glycols	26	1.3 (0.71–2.3)
	Ketones	21	0.71 (0.41–1.3)
Spina bifida			
Blatter et al., 1996	Occupational exposure (2 weeks before to 6 weeks after conception)		
	All organic solvents	29	0.9 (0.6–1.6)
Gastroschisis			
Torfs et al., 1996	Children born with gastroschisis		
	Maternal exposure from preconception through first trimester		
	All solvents, low exposure	13	2.28 (0.99–5.24)
	All solvents, high exposure	15	3.84 (1.61–9.17)
	Aromatic hydrocarbons, high exposure	9	4.74 (1.45–15.49)
	Glycols	6	2.00 (0.65–6.20)
Paternal exposure			
Spina bifida			
Blatter et al., 1997	Paternal occupational exposure (3 months before conception to 1 month after conception)		
	Solvents	29	0.7 (0.4–1.1)
	Low	19	0.6 (0.4–1.1)
	Moderate or high	10	0.9 (0.4–2.0)

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9

ADDITIONAL HEALTH EFFECTS

This chapter reviews the evidence concerning long-term, nonmalignant health outcomes that persist after cessation of exposure to insecticides or solvents. The immediate health effects of exposure to those agents are described in Chapters 3 and 4. In this chapter, a number of health outcomes are discussed with background information presented before the descriptions of epidemiologic studies. The committee considers case studies and case series for the health outcomes described in this chapter, because some of these outcomes may be difficult to investigate epidemiologically due to their rare occurrence or lack of reporting mechanisms (such as disease registries). For some health outcomes discussed in this chapter, such as renal effects, there is a body of literature only on exposure to solvents.

APLASTIC ANEMIA

Aplastic anemia is a disorder of hematopoiesis that occurs when the bone-marrow stem cells fail to produce mature blood cells. Some patients with aplastic anemia progress into myelodysplastic syndromes. Although aplastic anemia can occur at any age, it is most common in young adults and the elderly. About 1000 new cases are diagnosed each year in the United States (Castro-Malaspina and O'Reilly, 1998). The disease is more prevalent in Asia than it is in Europe or North America. In a small percentage of cases, aplastic anemia is an inherited condition (such as Fanconi's anemia). Risk factors for acquired aplastic anemia include exposure to certain drugs (such as chloramphenicol or sulfonamides), industrial chemicals (such as benzene), high doses of radiation, chemotherapy treatments, viral infections (such as Epstein-Barr virus), and immune diseases. However, for more than half the reported cases a cause cannot be determined.

Epidemiologic Studies of Aplastic Anemia and Exposure to Insecticides

Several studies have examined the risk factors for aplastic anemia in relation to exposure to insecticides and pesticides. In response to concerns about possible high rates of aplastic anemia in Thailand, a population-based, case–control study began in Bangkok in 1989 and was expanded in 1991 to include two rural regions of Thailand (Issaragrisil et al., 1996). Patients and control subjects were interviewed about medical and occupational histories, drug and pesticide use, and chemical and radiation exposures. Issaragrisil and colleagues (1997) examined grain farming and pesticide use in a study of 81 cases of aplastic anemia in Khonkaen, a rural region in Thailand. That study involved 295 control subjects selected from the same medical institutions where the cases had been identified. The researchers reported an increased risk associated with occupational pesticide exposure

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(relative risk [RR] = 2.7, 95% confidence interval [CI] = 1.1–6.6). For a subset (n = 10) exposed to organophosphate insecticides, there was an elevated but equivocal increase in risk (RR = 1.9, 95% CI = 0.6–5.9). The authors state that selection bias is improbable as an explanation for the associations because of the low refusal rate, but they do not discuss the limitation of hospital-based case–control studies in selecting control patients or the possibility of recall basis.

A companion study examined recent household insecticide use in the entire group of cases (n = 253) and controls (n = 1174) in Bangkok and in two rural regions of Thailand (Kaufman et al., 1997). Risk estimates were calculated for use of specific insecticides and for groups of insecticides, and multiple logistic regression analyses were used to control for confounding by concomitant use of more than one insecticide and for demographic variables. A moderate increase in risk was seen in the comparison of cases (n = 32) and controls (n = 117) that reported any exposure to an insecticide product that combined dichlorvos, propoxur, and cyfluthrin (a pyrethroid) (RR = 1.7, 95% CI = 1.1–2.8). However, for subsets of this exposure group, associations were increased but not statistically precise: regular use (RR = 1.6, 95% CI = 0.9–2.9) and application by the subject (RR = 1.8, 95% CI = 0.8–4.1). Evaluation of exposure to the classes of insecticides showed no trend with increasing exposure for the subsets that reported any exposure to carbamates (n = 36) (RR = 2.1, 95% CI = 1.2–3.7), regular use of carbamates (n = 19) (RR = 2.0, 95% CI = 1.0–4.1), or carbamates applied by the subject (n = 11) (RR = 2.3, 95% CI = 0.8–6.5). No important increases were seen in the analyses that examined exposure to classes of insecticides (organophosphates, pyrethrins, or organochlorines). The authors acknowledge that the few positive associations could have occurred by chance in the course of conducting multiple comparisons.

A case–control study of cases identified from the French national aplastic-anemia registry used interviews with 98 patients, 181 hospitalized control subjects, and 72 neighbor control subjects (Guiguet et al., 1995). Detailed information was collected about occupational history, including tasks, exposures, environmental conditions, and protection. Risk of aplastic anemia was not consistently elevated for occupational exposure to insecticides (n = 18) compared with hospitalized controls (odds ratio [OR] = 1.6, 95% CI = 0.8–3.0) or with neighbors (OR = 0.4, 95% CI = 0.1–1.3).

A case–control study in North Carolina evaluated the relationship between occupational pesticide exposure and fatal cases of aplastic anemia (Wang and Grufferman, 1981). Sixty deaths attributable to aplastic anemia were identified from state records; two controls that died in the same year were selected for each case. No relationship was found between deaths in cases with occupations that might have involved exposure to pesticides and the occurrence of aplastic anemia (RR = 0.67, 95% CI = 0.26–1.7). Unlike the studies from Thailand, subjects for this study were identified from death certificates rather than from a hospital-case registry, and occupations recorded on death certificates, rather than questionnaires, were used to evaluate potential exposure. The authors reported no relationship between trends in the use of organochlorine insecticides (including lindane) and the incidence of aplastic anemia.

A number of studies have examined the relationship between hematologic parameters and exposure to insecticides. Those studies have the potential to provide evidence to support conclusions on aplastic anemia; however, because they generally examined workers with continuing exposures, they do not provide information about

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persistent or long-term effects. For example, Bhatnagar and colleagues (1980) studied workers at a pesticide-formulation factory in Agra, India. They compared blood samples from 42 employees who manufactured DDT, aldrin, lindane, malathion, parathion, and carbaryl with blood samples from 15 healthy subjects chosen as controls. The pesticide-exposed workers had lower hemoglobin (11 g/dL vs 14.48 g/dL). No attempt was made to control for dietary iron intake, age, sex, or other medical conditions that could have been confounding factors. It also could not be ascertained whether the observed changes were short- or long-term effects. The committee reviewed many other hematologic studies, but they did not provide information on persistent long-term health effects (e.g., Khan and Ali, 1993; Milby and Samuels, 1971; Morgan and Lin, 1978; Queiroz et al., 1999; Rosenberg et al., 1999; Straube et al., 1999; Traczyk and Rudowski, 1979; Vine et al., 2000).

Summary and Conclusion

A small number of case–control studies have examined exposure to insecticides in relation to aplastic anemia (Table 9.1). One study showed increased risk associated with exposure to a mixture of dichlorvos, propoxur, and a pyrethroid. Other studies have not shown substantially increased risks for insecticide exposure.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and aplastic anemia.

TABLE 9.1 Selected Epidemiologic Studies: Aplastic Anemia and Exposure to Insecticides

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Case–control Studies			
Issaragrisil et al., 1997	Residents of rural Thailand		
	Organophosphate exposure	10	1.9 (0.6–5.9)
Kaufman et al., 1997	Residents of Thailand		
	Dichlorvos, propoxur, cyfluthrin		
	Any exposure	32	1.7 (1.1–2.8)
	Regular use	17	1.6 (0.9–2.9)
	Applied by subject	8	1.8 (0.8–4.1)
	Carbamates		
	Any exposure	36	2.1 (1.2–3.7)
	Regular use	19	2.0 (1.0–4.1)
	Applied by subject	11	2.3 (0.8–6.5)
Wang and Grufferman, 1981	Residents of North Carolina in pesticide-exposed occupations	60	0.67 (0.26–1.7)
Guiguet et al., 1995	Residents of France and insecticide exposure		
	Hospital control comparison	18	1.6 (0.8–3.0)
	Neighbor control comparison	4	0.4 (0.1–1.3)

Epidemiologic Studies of Aplastic Anemia and Exposure to Organic Solvents

Most of the relevant research on aplastic anemia has focused on exposure to benzene; a few studies have examined other specific solvents or solvent mixtures.

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Benzene

Exposure to benzene at high doses is hematotoxic and can result in destruction of bone-marrow precursor cells and, in turn, in a decrease in white-cell, red-cell, and platelet counts (Goldstein, 1988). The hematotoxicity and carcinogenicity of benzene have been extensively reviewed (e.g., ATSDR, 1997; IARC, 1987), and a brief overview of the toxicologic information is provided in Chapter 4. The metabolism of benzene, which occurs in the liver and to a lesser extent in the bone marrow, plays an important role in its toxicity. Benzene is metabolized to benzene oxide, an epoxide, through an oxidation reaction catalyzed primarily by cytochrome P450 2E1. Cytochrome P450 2E11/6 also participates in benzene biotransformation. Benzene oxide can then be metabolized to various compounds, including *o*-benzoquinone and *p*-benzoquinone, which are thought to be the two main metabolites that mediate the toxicity of benzene. Data from laboratory animals and humans show that benzene affects the bone marrow in a dose-dependent manner, causing anemia, leukopenia, and thrombocytopenia; continued exposure causes aplasia and pancytopenia[1] (Bruckner and Warren, 2001). Benzene also has carcinogenic properties. In experimental animals, an increased incidence of malignant lymphomas and some solid tumors have been seen after exposure to high doses of benzene. As discussed in Chapter 6, benzene has also been associated with some types of leukemia in humans.

Most of the human evidence associating benzene exposure with aplastic anemia comes from case studies (many published in the early to middle 1900s). Although exposure characterization methods were poor, it is estimated that benzene concentrations often exceeded 100 ppm[2] (as summarized in Smith, 1996). The hypothesis of an association with benzene exposure raised by the case reports has been confirmed by several epidemiologic studies, although most of the population-based studies have focused on the relationship between exposure to benzene and hematopoietic cancers (see Chapter 6).

As early as 1897, the deaths of four workers at a Swedish bicycle-tire factory were attributed to aplastic anemia associated with exposure to high concentrations of benzene (cited in Aksoy, 1985). A retrospective cohort study by Paci and colleagues (1989) examined exposures to potentially high concentrations of benzene among shoe-factory workers in Florence, Italy. During the period from 1953 to 1960, glues—estimated to be as much as 70% benzene by weight—were used in shoe manufacturing. When the researchers compared mortality rates for the 1950–1984 cohort of workers with national rates, they found increases for aplastic anemia in women (one case versus 0.2 expected) and in men (six cases versus 0.38 expected). The Italian national mortality rates combined all blood diseases, and the analysis resulted in standardized mortality ratios (SMRs) of 4.16 (95% CI not provided) for women and 15.66 (95% CI = 5.47–32.64) for men.

A retrospective cohort study examined hematopoietic malignancies and related disorders in a group of 74,828 workers in China who were employed in 1972–1987 in benzene-exposed departments of 672 factories (Dosemeci et al., 1994; Travis et al., 1994; Yin et al., 1996a,b). Mortality and morbidity data on this cohort were compared with data on 35,805 nonexposed workers employed during the same period. Physician investigators blinded to exposure information reviewed histopathologic information, pathology reports,

[1]Pancytopenia is a nonfatal condition with below normal values of red cells, white cells, and platelets.
[2]The allowable occupational-health standard for benzene has steadily decreased in the United States. In 1987, the permissible exposure limit (PEL) set by the Occupational Safety and Health Administration was reduced from 10 ppm to 1 ppm TWA (time-weighted average).

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and medical records of workers who developed hematologic neoplasms and related disorders. Yin and colleagues (1996a) reported nine cases of aplastic anemia in the benzene-exposed cohort as compared with no cases in the nonexposed population. Because the study used such a large population, it was possible to detect differences in relatively infrequent outcomes. Furthermore, there was a careful review of medical records to confirm the diagnoses. However, there is a possibility that the results were confounded by other occupational exposures.

Potential risk factors for aplastic anemia were examined in a case–control study in Baltimore, Maryland. Linet and colleagues (1989) compared 59 cases of aplastic anemia diagnosed in 1975–1982 with 59 controls matched for age, sex, race, and geographic area and selected by random-digit dialing. An increased risk of aplastic anemia was associated with self-reported benzene exposure (OR = 3.1, 95% CI = 1.0–9.2). However, for the purposes of this review, the inferences from the study are limited by the fact that 41% of the patients with aplastic anemia were under 20 years old at diagnosis and would not have had substantial occupational exposures.

Two other studies provide information on the relationship between benzene and aplastic anemia. In a case series from Turkey, Aksoy and colleagues (1984) reported that about 23% of patients with aplastic anemia had reported exposure to benzene. The study examined potential risk factors but did not have a comparison population. Ott and colleagues (1978) reviewed the deaths (1938–1970) of 594 workers chronically exposed to benzene at concentrations of 1 ppm to over 30 ppm at a Dow Chemical plant. One death from aplastic anemia was reported, whereas only 0.1 would have been expected.

The relationship between changes in hematologic parameters and exposure to low concentrations of benzene has been extensively studied. However, the studies generally are cross-sectional and do not provide substantial information about persistent or long-term effects of interest in this review, and they generally have had inconsistent findings. When changes were seen in hematologic measures at low exposure, the differences (such as in hematocrit, hemoglobin, white-cell count and platelet count) often were not internally consistent with other measures (for example, an elevated mean red-cell volume would be expected but decreased mean corpuscular hemoglobin concentration would not). Changes in hematologic or immunologic parameters are not necessarily stages in the development of a pathologic process. For example, the finding of gradually lower numbers of blood cells does not mean that continued exposure would lead to the development of aplastic anemia.

Examples of studies of hematologic parameters include the studies by Kipen and colleagues (Cody et al., 1993; Kipen et al., 1988, 1990) who followed a cohort of rubber workers exposed to varying concentrations of benzene. Studies of this cohort are described in Chapter 6 regarding cancer outcomes, particularly leukemia (Rinsky et al., 1981, 1987). During the period from 1940–1948, as benzene exposures gradually dropped from 137 ppm to 32 ppm, white-cell counts rose (from 6200 to 9591), red-cell counts rose (from 4.67 to 5.13), and hemoglobin rose (from 97.0 to 108.0) (Kipen et al., 1988). Those findings indicate that exposure to relatively high concentrations of benzene depressed the production of blood cells. In the years after 1948, when benzene exposure was much reduced, the values for white- and red-cell counts were within the normal ranges (although a nonexposed comparison group was not studied in the same period).

A study by Collins and colleagues (1991) compared hematologic parameters of 200 workers at a chemical factory who were exposed to low concentrations of benzene (0.01–1.4

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ppm) with those of 268 nonexposed workers from the same factory. The study found no abnormalities in white-cell count, red-cell count, hemoglobin concentration, platelet count, or mean red-cell volume. The study did find that smoking affected many hematologic parameters, underlining the importance of controlling for confounding. Many other studies of the effects of benzene exposure on hematologic parameters that were reviewed provided no information on persistent long-term health effects (e.g., Aksoy et al., 1971; Bogadi-Sare et al., 1995, 1997; Collins et al., 1997; Khuder et al., 1999; Rothman et al., 1996; Tsai et al., 1983; Ward et al., 1996).

Solvents

Only a few studies have examined aplastic anemia in relation to exposure to other specific solvents or to solvents in general. Several of the insecticide-exposure studies described above also examined exposure to solvents. The population-based, case–control study in Thailand (Issaragrisil et al., 1996) compared 284 cases of aplastic anemia identified in 40 hospitals in Bangkok and 15 hospitals in rural areas. The study enrolled four hospital controls of similar age and sex for each case. Two hematologists confirmed the diagnoses of aplastic anemia. Using interviews with the case and control subjects, the researchers examined several risk factors for aplastic anemia. For the cases and controls drawn from Bangkok hospitals, there was a strong association with a history of solvent exposure (RR = 4.6, 95% CI = 2.5–8.7). About 40% of the total cases came from rural hospitals, and no association was noted when those cases were compared with their controls. The study reported positive associations for other risk factors (such as grain farming, hepatitis A, and low socioeconomic status) and multivariate analyses adjusted for the many possible confounders. However, the study presents little information on exposure-assessment methods, participation rates, or the conduct of the interviews. Also, such hospital-based case–control studies are vulnerable to selection and recall bias.

Using the French national register of aplastic anemia, Guiguet and colleagues (1995) studied 98 patients with aplastic anemia (recorded in the register in 1985–1988) and two groups of controls: 181 selected from the same hospital as the cases and 72 referred by case patients from among neighbors. Interviews were conducted to determine occupational and medical histories, and a toxicologist coded the occupational exposures (any exposure or a "large level of exposure"). The study reported no association between aplastic anemia and exposure to all types of solvents compared with hospital controls (OR = 0.9, 95% CI = 0.5–1.7) or neighbor controls (OR = 0.6, 95% CI = 0.3–1.4). Analysis of exposure to various classes of solvents revealed no consistently increased risk; for example, for higher exposure to halogenated solvents, the OR was 1.3 (95% CI = 0.6–2.7) compared with hospital controls. Although the study was limited by a 50% participation rate, interviews were conducted at diagnosis, and the investigators found no evidence of participation bias in the case group.

The case–control study in Baltimore, Maryland, described above (Linet et al., 1989) found an association of aplastic anemia with self-reported exposure to paint (OR = 6.1, 95% CI = 1.2–29.7), but there was no association with the occupation of painter. The study reported a slightly elevated risk for aplastic anemia and exposure to any solvents (OR = 1.1, 95% CI = 0.5–2.7). However, as noted above, the inferences from this study are limited by the fact that 41% of the patients with aplastic anemia were under 20 years old at diagnosis and would not have experienced substantial occupational exposure.

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Although a number of studies of the effects of exposure to solvents, particularly ethylene glycol ethers, on hematologic parameters were reviewed, the studies did not provide information on the persistent, long-term health effects of concern in this report (e.g., Cardoso et al., 1999; Cook et al., 1982; Cullen et al., 1983, 1992; Kyvik et al., 1992; Shamy et al., 1994; Shih et al., 2000; Welch and Cullen, 1988).

Summary and Conclusion

The hematotoxicity of benzene's metabolites has been well characterized in animal studies with strong evidence of a dose-response relationship. For more than a century, case studies have reported a direct association between chronic high-level exposure to benzene and aplastic anemia in humans. This association has been confirmed in studies of workers exposed to potentially high concentrations of benzene that found consistently increased risks of aplastic anemia (Table 9.2). The effects of low-level benzene exposure, however, have not been studied as fully, and there have been inconsistent findings regarding changes in hematologic parameters in studies of low level occupational exposure to benzene. Studies of exposure to solvent mixtures have not revealed consistent increased associations with aplastic anemia.

Results are for cases with higher exposure as compared with hospital controls.The committee concludes, from its assessment of the epidemiologic and experimental literature, that there is sufficient evidence of a causal relationship between chronic exposure to benzene and aplastic anemia.

There is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to other specific organic solvents under review or solvent mixtures and aplastic anemia.

TABLE 9.2 Selected Epidemiologic Studies: Aplastic Anemia and Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Benzene			
Cohort Studies			
Paci et al., 1989	Shoe-manufacturing workers in Florence, Italy		
	Females	1	4.16[a]
	Males	6	15.66 (5.47–32.64)[a]
Yin et al., 1996	Workers in China	9	Indeterminate[b]
Linet et al., 1989	Residents of Baltimore, Maryland	13	3.1 (1.0–9.2)
Solvents			
Case–control Studies			
Issaragrisil et al., 1996	Residents of Thailand		
	Bangkok residents	NA	4.6 (2.5–8.7)
Guiguet et al., 1995	Residents of France		
	All types of solvents	27	0.9 (0.5–1.7)[c]
	Halogenated solvents	16	1.3 (0.6–2.7)[c]
	Hydrocarbon solvents	19	1.2 (0.6–2.3)[c]

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Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Linet et al., 1989	Residents of Baltimore, Maryland		
	Any solvents	12	1.1 (0.5–2.7)

NOTE: NA = not available.
[a]SMR was calculated for bloodborne diseases as a group.
[b]Study reported no nonexposed workers with aplastic anemia.

CARDIOVASCULAR EFFECTS

Cardiovascular disease is among the most common causes of death, chronic illness, and disability among adults in the United States. Most of the risk factors are related to lifestyle and family history, but occupational and environmental risk factors have been suggested for several cardiovascular outcomes. A potential for increased risk of ischemic heart disease is attributable to chronic exposure to carbon disulfide used in rayon manufacturing, and risk of cardiac arrhythmia is attributable to acute exposure to high concentrations of solvents (Fine, 1992; Kurppa et al., 1984). Exposure to some heavy metals, such as lead, also has been associated with the potential for intermediate cardiovascular outcomes, such as hypertension (Kristensen, 1989).

Epidemiologic Studies of Cardiovascular Effects and Exposure to Insecticides

The cardiac effects of the insecticides and insect repellents examined in this report have been discussed in the literature primarily in the context of acute poisoning (Roth et al., 1993; Saadeh et al., 1997). However, the insecticide literature is sparse regarding long-term cardiovascular health outcomes.

Two studies examined hypertension in relation to exposure to insecticides and other pesticides. A study in Oregon reported no difference in average blood pressure between control subjects and workers who formulated phenoxy herbicides or other unspecified pesticides (Morton et al., 1975); it was limited by a lack of information about the degree of exposure among the participating workers. Sandifer and colleagues (1972) reported increased systolic blood pressure among pesticide formulators and pest-control operators but not among farmers, manufacturing workers, workers designated as peripherally exposed, and control subjects. Both studies examined workers currently exposed to pesticides, so it was not possible to separate long-term and short-term health effects.

Evaluation of the long-term cardiovascular effects of exposure to insecticides was limited to data from mortality studies done primarily for purposes of assessing cancer risk. Many studies focused on pesticides in general and provided sparse exposure information. Most studies showed decreased cardiovascular mortality or no association but did not control for confounding by risk factors, such as smoking, family history of cardiac disease, and diet. The studies also were potentially limited by a selection bias known as the healthy-worker effect (see Chapter 2). For example, a study of 32,600 employees at a lawn-care service that used insecticides (including diazinon, carbaryl, and malathion), herbicides, and fungicides reported 17 deaths from arteriosclerotic heart disease (including congestive heart disease) (Zahm, 1997). Comparable US population mortality rates would project an expected 33.1 deaths (SMR = 0.51, 95% CI = 0.30–0.82). The cohort was generally young

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and had been employed for only a short period (mean = 1.6 years). Pesatori and colleagues (1994) reported similar results for mortality in a cohort of 4411 structural pest-control workers in Florida. For deaths from arteriosclerotic heart disease, the SMR was 0.9 (95% CI = 0.5–1.1).

Summary and Conclusion

Although a well-recognized complex of short-term, reversible cardiac effects is associated with some pesticide poisonings, there are few data on long-term cardiovascular outcomes. Data from cross-sectional studies of workers who have continuing exposure to insecticides do not offer insights into the long-term nature of the effects. Mortality studies of pesticide-exposed workers show no increased risk; however, the healthy-worker effect and other study limitations make it difficult to evaluate long-term outcomes.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and irreversible cardiovascular outcomes.

Epidemiologic Studies of Cardiovascular Effects and Exposure to Organic Solvents

The literature on cardiovascular effects of solvent exposure is primarily on the short-term consequences of acute exposure. For some solvents, short-term cardiovascular effects are known to occur following acute exposure (reviewed in Kristensen, 1989; Wilcosky and Simonsen, 1991). For example, a body of medical literature, primarily case reports, exists regarding the metabolism of methylene chloride to carbon monoxide and the later development of angina pectoris in susceptible persons as a result of increases in carboxyhemoglobin. Case reports also discuss cardiac sensitization and arrhythmia attendant on acute exposure to chlorofluorocarbons and, to a smaller degree, to chlorinated solvents. Since these effects are considered short-term and they occur soon after exposure, they would not be considered relevant for the time frame being considered for Gulf War veterans.

The committee examined many cohort mortality studies that assessed excess mortality (usually with a focus on discerning elevations in cancer) among workers known to have been occupationally exposed to a variety of solvents. For the most part, the studies showed no effect or a decrease in cardiovascular diseases among the workers. Because of their study design, those studies do not control for the healthy-worker effect or for confounding attributable to cigarette smoking or other confounding factors. Due to the limitations in this type of study design for the purposes of this review, the studies are not reviewed in detail here. A meta-analysis by Chen and Seaton (1996) assessed 52 published mortality studies of occupational solvent exposure and calculated a pooled SMR of 0.87 (95% CI = 0.86–0.88) for all circulatory disease. Although the committee did not include meta-analyses in the body of evidence it used for making a conclusion, that study provides an indication of the extent to which the healthy worker effect pervades the evidence related to cardiovascular outcomes.

In a cross-sectional study, Kotseva and Popov (1998) examined cardiovascular effects attributable to occupational exposure to solvents (including benzene, xylene, and phenol) in a Bulgarian petrochemical factory. The study identified 345 workers and 345 age-

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and sex-matched control subjects and divided them into three categories: highest benzene, toluene, and gasoline exposures; high xylene and lower toluene, benzene, and gasoline exposures; and exposure primarily to phenol. Meaningfully higher prevalences of electrocardiographic abnormalities and higher mean systolic and diastolic blood pressure as compared to the controls were found among the exposed members of the first two groups, but not among those exposed primarily to phenol. Given the study design, the workers were being exposed to solvents occupationally at the time of the study and so were not considered exposure-free for the evaluation of persistent effects.

A retrospective cohort mortality study of workers at a cellulose-fiber plant examined ischemic heart disease (IHD) in 1271 workers exposed to methylene chloride (Ott et al., 1983). The study did not report an increase in IHD mortality among workers compared with the general population, nor when the duration of exposure and followup interval for IHD were assessed. A study of male workers exposed to methylene chloride in the production of cellulose triacetate photographic-film base also did not find an increased risk of IHD (Hearne et al., 1990).

Suadicani and colleagues (1995, 1997) reported on the Copenhagen Male Study, which began in 1970 as a prospective cardiovascular cohort study of 2974 men who were free of IHD at the study's outset. At the time of the analysis, 184 men had had at least one IHD event; 258 members of the cohort reported occupational exposure to organic solvents. The adjusted RR comparing men exposed to solvents with unexposed men was 1.7 (95% CI = 1.1–2.7). The occupational exposure assessment in this study was based on self-assessment of lifetime occupational exposure, which could lead to recall and misclassification bias. No information is provided about the timing of exposure and the development of myocardial infarction.

Wilcosky and Tyroler (1983) examined mortality from heart disease among workers exposed to solvents in a rubber and tire manufacturing plant in Akron, Ohio. They identified 1282 white male, hourly-wage workers who were employed at the plant or had retired after at least 10 years of exposure. Exposure estimates were obtained from annual solvent-use charts prepared for major processing areas of the plant for 25 solvents. Each subject was identified as having been exposed to specific solvents through a review of which jobs he had held in the company and through a review of the list of solvents authorized for use in specific areas, according to the annual-use charts. Until 1967, the plant had authorized the use of carbon disulfide, known to be associated with atherosclerosis (and not among the solvents sent to the Gulf War). Most workers were exposed to more than one solvent, and several solvents were often used concurrently in the process areas. Several solvents showed associations with IHD mortality, but the associations were inconsistent when adjusted for age and other solvent exposures. The age-adjusted rate ratio for workers exposed to ethanol but not to carbon disulfide or phenol was 1.8; for workers exposed to phenol but not carbon disulfide or ethanol, it was also 1.8. The study did not control for confounding by other known cardiovascular risk factors, and misclassification of exposures probably occurred. The authors pointed out that "solvent authorization" did not necessarily guarantee solvent use.

As a part of the Stockholm Heart Epidemiology Program, Gustavsson and colleagues (2001) identified 1335 persons surviving for at least 28 days after a first myocardial infarction. Control subjects were selected from a population registry and were sex-, age- and catchment-area-matched with the case subjects. Subjects were asked to complete

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questionnaires on lifetime occupational history, including descriptions and duration of work. An industrial hygienist assigned exposure levels on the basis of probability and intensity. Adjusting for age, sex, smoking, hypertension, weight, diabetes mellitus, and physical activity, the authors reported a RR estimate for organic solvent exposure of 1.26 (95% CI = 1.02–1.55) for those with low exposure, 1.05 (95% CI = 0.76–1.47) for medium exposure, and 1.49 (95% CI = 0.94–2.35) for the highest category of exposure compared with the unexposed subjects. The analysis of exposure and duration showed no trend with increasing exposure (lowest exposure, RR = 1.50, 95% CI = 1.14–1.96; moderate exposure, RR = 1.00, 95% CI = 0.74–1.34; and highest exposure, RR = 1.20, 95% CI = 0.92–1.58). The authors performed additional analyses to account for latency periods and lag in the calculation of dose, but the models gave no closer fit to the data. Variations of exposure within similar jobs and errors in work-history information could have contributed to exposure misclassification.

Summary and Conclusion

Only a few studies on solvent exposure have examined long-term cardiovascular effects, and they show inconsistent results and no trend of increased risk with increasing estimated exposure. Cohort mortality studies have generally demonstrated decreases in cardiovascular disease, but do not account for the healthy-worker effect. Other occupational cohort and case–control studies are fraught with the difficulties of assigning subjects in a retrospective exposure assessment and of controlling for lifestyle and other risk factors.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the specific organic solvents under review or solvent mixtures and irreversible cardiovascular outcomes.

RESPIRATORY EFFECTS

Many compounds that are used in industry or have been identified as environmental contaminants have been associated with the development of nonmalignant lung disease. Examples are chronic bronchitis and emphysema associated with cigarette smoking, asthma associated with toluene diisocyanate exposure, and pulmonary edema associated with exposure to chlorine gas. The major confounding factor in most occupational studies of respiratory outcomes is smoking. Exposure to dusts and various chemical compounds also must be considered. For example, although some agriculture-related respiratory diseases have a known etiology (such as silo filler's disease, which results from inhalation of nitrogen dioxide in unventilated farm silos), it has not been possible to pinpoint the etiology of many respiratory effects from among the numerous agricultural exposures of concern, including dusts, fungi, pesticides, and fertilizers (do Pico, 1992).

The literature on respiratory effects includes cross-sectional studies that examined lung function in relation to insecticide or solvent exposure. Often, the subjects were employed at the time lung function was assessed and so had ongoing exposures to the compounds of concern. Thus, it was often not possible to assess the persistence of changes in lung function after exposure had ended.

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Case–control and cross-sectional studies of Gulf War veterans have reported a high prevalence of respiratory symptoms (Cherry et al., 2001; Gray et al., 1999; Proctor et al., 1998; Richards et al., 1993), asthma (Gray et al., 2000), airflow obstruction and chronic laryngotracheitis (Das et al., 1999), and sleep apnea (Peacock et al., 1997) (see Appendix A). Those studies did not examine the association between the outcomes and specific Gulf War exposures to insecticides or solvents.

Epidemiologic Studies of Respiratory Effects and Exposure to Insecticides

A small number of studies have examined the persistent, long-term respiratory effects of exposure to insecticides. Acute high-level exposures to organophosphate compounds can result in an acute cholinergic syndrome involving bronchospasms (see Chapter 3). However, few studies have examined long-term respiratory outcomes related to insecticide exposures. Kossmann and colleagues (1997) conducted a cross-sectional study of 37 male and 17 female workers in the division of a chemical plant that produced liquid and dust pesticides. Those workers were exposed to multiple compounds, including organophosphate insecticides (such as dichlorvos), pyrethroids, triazines, carbamates, and dithiocarbamates. A control group of 22 men and 15 women, residents of the same region, were not occupationally exposed to chemical agents. The chemical-plant workers showed a 50% prevalence of chronic bronchitis, but this outcome was not assessed in the controls. Spirometry tests revealed obstructive impairment of pulmonary function in 11% of the chemical-plant workers. Peak expiratory flow was diminished in 41% of females and 27% of males. A strong correlation between decreased peak expiratory flow and the force of expiratory muscles was observed that could have been the result of muscle weakening caused by exposure to organophosphate compounds. The study was limited for the purposes of this review by its cross-sectional design and by the continuing exposure of the subjects to insecticides and pesticides. An attempt was made to control for the effect of smoking, but the group was too small to control for the confounding effect of multiple exposures.

A cross-sectional study of farmers in Saskatchewan described the prevalence of self-reported asthma and its possible association with the use of insecticides and herbicides (Senthilselvan et al., 1992). An internal comparison group of nonexposed farmers was compared with pesticide-exposed members of the cohort, controlling for age, smoking pack-years, and nasal allergies. Of 2375 farmers who were contacted, 1939 (81.6%) responded to a questionnaire and completed a pulmonary-function test (PFT). The validity of the self-reported diagnosis was supported by the finding that self-identified asthmatics had lower mean values of PFT variables than did self-identified non-asthmatics. An increased prevalence of asthma was associated with the use of carbamate insecticides (including methomyl and carbaryl) (adjusted OR = 1.8, 95% CI = 1.1–3.1). The study was limited by its partial reliance on subjective questionnaire data, by possible selection bias, and by confounding by noninsecticidal occupational exposures.

Other cross-sectional studies have reported positive associations between respiratory symptoms or impairment and exposure to insecticides (Al-Shatti et al., 1997; Rastogi et al., 1989; Sprince et al., 2000; Zuskin et al., 1997b), but they did not examine the persistence of outcomes after exposure had ended.

Cohort mortality studies have generally not reported an increase in nonmalignant respiratory disease mortality in cohorts of workers in pesticide-related occupations. Considerations regarding these studies include the healthy-worker effect, difficulties in

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using death certificates to account for nonmalignant respiratory disease, and the overwhelming effects of smoking, which are difficult to control for adequately. Other workplace respiratory hazards also could confound results. A study of 2384 workers at a pesticide-manufacturing plant in Colorado that produced dichlorvos, aldrin, and other pesticides reported that the overall rate of deaths attributable to nonmalignant respiratory disease was not elevated over that of the state's general population (SMR = 1.07, 95% CI = 0.78–1.43) (Amoateng-Adjepong et al., 1995). There was an increase in deaths from pneumonia (20 compared with 13 expected), which the authors hypothesized could have resulted from exposure to respiratory irritants (such as chlorine and bromine) at the plant. Zahm (1997) studied mortality in pesticide applicators and other employees of a lawn-care company who handled herbicides, fungicides, and insecticides (including malathion, chlorpyrifos, carbaryl, and diazinon). The SMR for nonmalignant respiratory disease was 0.67 (based on eight deaths). Other mortality studies of pesticide applicators and workers exposed to insecticides (and other pesticides and chemicals) showed no increase in deaths from nonmalignant respiratory disease (Alavanja et al., 1987, 1990; Blair et al., 1983; Fleming et al., 1999; Littorin et al., 1993; MacMahon et al., 1988; Pesatori et al., 1994; Wang and MacMahon, 1979).

Summary and Conclusion

The body of evidence on nonmalignant respiratory outcomes and insecticide exposures consists primarily of cross-sectional studies on lung function that did not examine long-term persistent outcomes after cessation of exposure. Furthermore, many studies did not control for confounding by smoking and other common causes of lung disease.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and persistent respiratory symptoms or impairment after cessation of exposure.

Epidemiologic Studies of Respiratory Effects and Exposure to Organic Solvents

Acute solvent exposure is generally recognized as causing acute mucosal irritation of the eyes, nose, and upper airways and symptoms of eye irritation, cough, and dyspnea that improve after exposure ends (reviewed in De Raeve and Nemery, 1999; Schenker and Jacobs, 1996). Rare case reports have described acute pulmonary edema or chemical pneumonitis after (frequently accidental) acute exposure to a small number of solvents, including formaldehyde, xylene, and styrene. Persistent nonspecific airway hyperreactivity or reactive-airway dysfunction syndrome (RADS) has been reported after exposure to high concentrations of a few organic solvents in a small number of case reports (Boulet, 1988; Brooks et al., 1985; reviewed in De Raeve and Nemery, 1999). In those cases, the subjects became acutely symptomatic within hours of the high level exposure. Symptoms and airway hyperresponsiveness usually resolve after the exposure ends, but they can persist for months to years. The delayed development of respiratory symptoms or the worsening of lung function months or longer after exposure has not been reported. The acute effects of exposure to lower occupational concentrations of solvents are less clear. A few studies have shown small decrements in lung function during the work shift or in exposure chambers;

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other studies have shown no acute effects. Solvents in general are not considered sensitizing agents and so are not considered a cause of immune-mediated asthma. The limited number of chamber studies with asthmatic volunteers generally has not shown acute effects of solvent exposure on lung function in those with underlying asthma (reviewed in De Raeve and Nemery, 1999; Schenker and Jacobs, 1996).

Cross-sectional studies have investigated the effects of solvent exposure on upper respiratory symptoms, comparing solvent-exposed workers with various control groups. Those studies have involved mixed solvent exposures in conjunction with exposures to substances that are known to cause respiratory effects, including reactive and irritant chemicals, metal fumes, agricultural products, and mineral dusts. More than half have shown a higher prevalence of respiratory symptoms—such as cough, wheezing, or dyspnea—in exposed workers than in control subjects (e.g., Kilburn, 1999; Lebowitz, 1977; McCurdy et al., 1995; Sabroe and Olsen, 1979; Talini et al., 1998; Zuskin et al., 1997a). However, almost all the studies involved workers with continuous exposure, so it was difficult to isolate persistent respiratory symptoms after the cessation of exposure.

A smaller number of cross-sectional studies of exposed workers have reported spirometry findings. Most did not reported differences between solvent-exposed workers and control subjects (e.g., Akbar-Khanzadeh and Rivas, 1996; Angerer et al., 1991; Lee et al., 1997; Talini et al., 1998). A few studies have reported reduced lung function in terms of forced expiratory volume or forced vital capacity (FEV_1, FVC, or FEV_1–FVC) in solvent-exposed workers when compared with a control group (Oleru and Onyekwere, 1992; White and Baker, 1988). However, solvent exposures generally occurred in conjunction with other, better-recognized respiratory hazards (metals, other chemical compounds, and irritants), and the control groups generally were not comparable. Also, those studies did not distinguish between acute and chronic exposure. No longitudinal followup studies of workers after cessation of exposure were identified.

Several community-population-based studies have investigated the association between exposure to occupational solvents and increased prevalence of respiratory symptoms, respiratory disease, or decreased lung function (Le Moual et al., 1995; Lebowitz, 1977; Post et al., 1994). During the 25-year followup of a group of male residents of the town of Zutphen in the Netherlands, the cohort received several medical examinations, and the morbidity and mortality of the cohort were followed. Post and colleagues (1994) examined chronic nonspecific lung disease in the cohort and found an increased risk with occupational solvent exposure (RR = 1.66, 95% CI = 1.14–2.41). A community population study of men in Tucson, Arizona, reported an increased prevalence of respiratory symptoms and reduced lung function in those exposed to solvents, smoke, and other substances (Lebowitz, 1977). Similar studies of asthma patients and of twins who had asthma have shown an increased risk of asthma with solvent exposures (Antti-Poika et al., 1992; Toren et al., 1999). However, the exposure assessments in those studies relied on self-reported occupational histories, and concurrent non-solvent exposures were common.

Mortality studies generally have not reported increases in nonmalignant respiratory disease mortality among solvent-exposed workers, and many have actually found reduced SMRs, which is probably a consequence of the healthy-worker effect (e.g., Hearne and Pifer, 1999; Lanes et al., 1990; Spirtas et al., 1991; Svensson et al., 1990; Walker et al., 1993). Other limitations of those mortality studies include difficulties in using death

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certificates to ascertain nonmalignant respiratory diseases, the overwhelming effects of smoking, and potential confounding by exposure to other non-solvent respiratory hazards.

Sleep apnea or nocturnal oxygen desaturation also has been examined in solvent-exposed workers (Edling et al., 1993; Laire et al., 1997; Monstad et al., 1987, 1992). Known risk factors for sleep apnea include obesity and alcohol and medication use. All the studies reported an increased prevalence of oxygen desaturation or sleep apnea in solvent-exposed workers. However, the control groups were rarely comparable, and known risk factors, such as obesity, were not often adequately addressed. One study (Monstad et al., 1992) found less sleep apnea when the subjects were retested 2 weeks after exposure; this suggests that the effect is more acute than chronic, which is similar to the effect of alcohol use on sleep apnea.

Summary and Conclusion

A few clinical and epidemiologic studies have evaluated associations between solvent exposure and respiratory symptoms, lung function (determined primarily with spirometry), nonmalignant respiratory diseases, and sleep apnea. Most have investigated the effects of acute exposure and generally have not differentiated persistent effects of exposure from short-term effects. Population-community-based studies have been hampered by basing exposure assessments on self-reports of occupational history. Occupational mortality studies of solvent-exposed workers, designed primarily to investigate cancer outcomes, are markedly limited in their ability to investigate nonmalignant respiratory outcomes because they use death certificates to ascribe respiratory mortality and morbidity. Furthermore, those studies are not able to control adequately for confounding by smoking or non-solvent occupational respiratory exposures. The healthy-worker effect may also limit the findings of the studies for the purposes of this report. Most studies involved mixed-solvent exposures, frequently in conjunction with other, better-known respiratory hazards, such as exposure to reactive and irritant chemical compounds, metal fumes, agricultural products, or mineral dusts. Although solvent exposure has only rarely been linked to RADS, it is conceivable that RADS resulting from acute, high-concentration exposure to solvents could persist for years after exposure. It is important to note that symptoms would appear at the time of exposure or shortly after.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between high-level exposure to mixtures of organic solvents and reactive airways dysfunction syndrome, which would be evident with exposure and could persist for months or years.

There is inadequate/insufficient evidence to determine whether an association exists between exposure to the specific organic solvents under review or solvent mixtures and persistent respiratory symptoms or impairment after cessation of exposure.

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HEPATIC EFFECTS

The liver is the major site for the metabolism of exogenous substances, such as drugs and other chemical compounds. This section examines three hepatic effects: changes in liver function, fatty liver (steatosis), and cirrhosis. Many blood tests are available for evaluating hepatotoxicity and liver disease; measures of the hepatic enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are often used because these enzymes are present at increased concentrations after acute liver injury or in hepatitis attendant to viral infection, chemical exposure, alcohol use, or use of some medications. The magnitude and pattern of transaminase increase can be helpful in distinguishing alcohol-induced injury from other causes of hepatotoxic effects, such as exposure to solvents. The AST:ALT ratio is almost always over 1 in alcohol-related injury; other toxicant- or virus-induced hepatic injuries usually result in an AST:ALT under 1 (Guzelian et al., 1988; Podolsky and Isselbacher, 1998; Redlich et al., 1990; Upfal et al., 1992). Additional serum markers include alkaline phosphatase, γ-glutamyl transpeptidase (GGT), and bilirubin. However, the sensitivity and specificity of the enzymes for liver disease vary. Biochemical tests (such as for fasting serum bile acids) can be used to assess various functions of the liver, although the clinical significance of the findings can be equivocal. Furthermore, liver disease (particularly chronic liver injury) can be present despite normal results of liver-function tests. Abnormal test results can be caused by alcohol or medication use, viral infection, diabetes, and nonhepatic disease. Despite those limitations, liver-function tests are the best noninvasive means of detecting liver injury and disease.

Fatty change in the liver, or steatosis, occurs in association with several clinical conditions, including alcohol-related liver disease, diabetes mellitus, hypertriglyceridemia, and obesity. It is also associated with the use of various medications, and it can be a normal variant. Some degree of steatosis accompanies acute liver injury and hepatic necrosis, and more marked steatosis commonly is seen in chronic toxin-induced liver injury. The difficulty of documenting steatosis greatly hinders epidemiologic studies. Patients are usually asymptomatic, and results of liver-function tests can be normal. Noninvasive evaluation of the liver with ultrasonography and computed tomography (CT) can suggest hepatic steatosis, but definitive diagnosis depends on histopathologic examination of a liver biopsy specimen. It is not clear how often steatosis progresses to cirrhosis (Neuschwander-Tetri and Bacon, 1996).

Cirrhosis, or end-stage liver disease, is a chronic, irreversible condition in which the normal lobular architecture is replaced with fibrous tissue and regenerating liver nodules. Common causes of cirrhosis are alcohol-related liver disease and viral infection.

Epidemiologic Studies of Hepatic Effects and Exposure to Organic Solvents

As discussed in this section, studies on exposure to solvents and hepatic outcomes were limited for the purposes of this review. Some solvents (particularly carbon tetrachloride) that are not topics of this report have known effects on the liver, but few studies on other solvents have examined long-term hepatic outcomes after exposure has ended.

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Liver Function

Case reports and case series have documented that high (frequently accidental) acute and subchronic exposure to some solvents—including 1,1,1-trichloroethane, tetrachloroethylene, and methylene chloride—can cause acute hepatotoxicity (chemical hepatitis), typically with increased aminotransferases, that improves when the exposure ends (reviewed in Baker, 1994). Aminotransferase concentrations usually return to normal (reviewed in Redlich et al., 1990). Chronic sequelae of such acute and subchronic exposures are not well documented.

The effects of subchronic and chronic exposure to typically lower concentrations of solvents have been harder to evaluate. Clinical and cross-sectional studies have reported the results of various liver-function tests in chronically exposed workers (such as painters and dry-cleaning workers), most of whom are exposed to mixtures of solvents and other chemicals. Most of those studies have demonstrated normal aminotransferases (Cai et al., 1991; Chia et al., 1987; Franco et al., 1986; Kurppa and Husman, 1982; Lundberg and Hakansson, 1985; Rees et al., 1993).

Mildly elevated GGT or aminotransferase concentrations in association with solvent exposure have been reported in a few cross-sectional studies (Chen et al., 1991; Guzelian et al., 1988; Tomei et al., 1999; Upfal, 1992). However, the studies do not differentiate past from current, continuous solvent exposure, so it is difficult to distinguish long- and short-term effects. The differences in liver-function tests between the exposed and control groups in the studies were small, and the increased values usually were within normal limits. The studies generally used small groups, and many had few details regarding the exposure. Further, there are few data to determine whether abnormal liver transaminases persist after removal from subchronic or chronic exposure, although some clinical reports suggest improvement (Cotrim et al., 1999).

Hepatic Steatosis

It is known that acute high exposure to solvents (particularly chlorinated hydrocarbons such as chloroform and carbon tetrachloride[3]) can result in hepatic injury, including necrosis (Bruckner and Warren, 2001). A limited number of case reports and case series suggest that chronic exposure to chlorinated solvents, such as 1,1,1-trichloroethane (Hodgson et al., 1989); to nonchlorinated solvents, such as toluene (Guzelian et al., 1988) and dimethylformamide (Redlich et al., 1990); and to mixed solvents (Dossing et al., 1983) can result in hepatic steatosis, which can persist after exposure ends (Dossing et al., 1983; Redlich et al., 1990).

Larger clinical studies also suggest that chronic solvent exposure is associated with hepatic steatosis. Cotrim and colleagues (1999) screened 1500 asymptomatic petrochemical workers in Brazil. The workers were exposed to a number of solvents, including benzene, toluene, xylene, and methanol. Workers with obesity, alcohol use, and other risk factors for steatosis were excluded. Liver biopsies were performed on 32 workers who met diagnostic criteria, including multiple test results of elevated liver enzymes. Twenty of the biopsied workers were diagnosed with nonalcoholic steatohepatitis. Eight to 12 months after the

[3]Because carbon tetrachloride was not among the solvents sent to the Gulf War, it is not reviewed in this report.

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exposure ended, the steatosis had improved in some, but not all, of those removed from exposure.

Brodkin and colleagues (1995) compared hepatic parenchymal echogenicity on ultrasonography and serum transaminase concentrations in 20 dry-cleaning operators exposed to tetrachloroethylene and in a control group of 29 nonexposed laundry workers. They reported that changes seen in ultrasonography consistent with steatosis were most strongly associated with high tetrachloroethylene exposure from the use of older dry-cleaning equipment and processes (OR = 4.2, 95% CI = 1.1–15.3). Mean ALT, AST, and GGT concentrations were somewhat higher in dry cleaners than in laundry workers. A case–control study in Sweden (Lundqvist et al., 1999) compared the occupational exposures of 30 men with steatosis with those of 120 control subjects in the same age range. Exposure to solvents was determined by questionnaire, and occupational-medicine physicians categorized the exposures. The study reported an OR of 4.3 (95% CI = 1.2–15) for mixed-solvent exposure and an increased risk for intense solvent exposure of 7.7 (95% CI = 1.7–48) for those who had been exposed for more than 1 year (in the preceding 15 years). A review of medical records ruled out confounding by alcohol use and other exposures.

Cirrhosis

There have been isolated often not well-documented case reports of cirrhosis associated with repeated exposure to several of the solvents reviewed in this report, including 1,1,1-trichloroethane and trichloroethylene (Thiele et al., 1982).[4] Increased mortality due to cirrhosis has been noted in several cohorts of workers with mixed solvent and other exposures, including highway and other maintenance workers (Maizlish et al., 1988), automobile mechanics (Schwartz, 1987), newspaper pressworkers (Paganini-Hill et al., 1980), and metal workers (Mur et al., 1987; Teta and Ott, 1988). The studies did not adequately account for possible confounding factors, such as alcohol use, viral hepatitis, and other non-solvent exposures.

Summary and Conclusion

Case reports have examined acute hepatotoxicity after high exposure that typically improved when the exposure ended. Clinical and cross-sectional studies have reported inconsistent findings from various liver-function tests in workers chronically exposed to solvents, many of whom likely had continuous solvent exposure. There are few data on the persistence of abnormal liver transaminases after subjects were removed from subchronic or chronic exposure. There is more-consistent evidence from clinical and case–control studies of an association between chronic solvent exposure and steatosis (Table 9.3). In most of those studies, the exposures occurred in industrial settings and involved exposures to mixed solvents over periods of years. Information on the relationship between cirrhosis and solvent exposure is limited to mortality studies, many of which were designed to examine multiple cancer outcomes and most of which did not account for alcohol use, exposures to substances other than solvents, and other potential confounders.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to specific organic solvents under

[4]Other solvents, particularly carbon tetrachloride, have also been associated with cirrhosis.

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review or solvent mixtures and cirrhosis or persistent alterations in liver function tests after cessation of exposure.

There is limited/suggestive evidence of an association between chronic exposure to solvents and hepatic steatosis that could persist after cessation of exposure.

TABLE 9.3 Selected Epidemiologic Studies: Hepatic Steatosis and Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Brodkin et al., 1995	Dry-cleaning workers in Seattle		
	Hepatic parenchymal changes and tetrachloroethylene exposure		
	Crude exposure	NA	2.5 (0.6–10.1)[a]
	Old dry- or wet-transfer operation	NA	4.2 (1.1–15.3)[a]
	Cumulative		
	<10 process-adjusted years	NA	5.1 (0.8–33.1)[a]
	≥10 process-adjusted years	NA	1.2 (0.2–7.2)[a]
Lundqvist et al., 1999	Male steatosis patients in Sweden		
	Intense exposure to solvents at anytime	6[b]	6.7 (1.4–30)
	in 1 year of preceding 15 years	6[b]	7.7 (1.7–48)
	in >5 years of preceding 15 years	6[b]	29.7 (3.2–218)

NOTE: NA = not available.
[a]Adjusted for age, alcohol consumption, body-mass index, sex, and serologic evidence of hepatitis.
[b]Data are for the highest exposure group as determined from type of job, title, and questionnaire exposure information.

GASTROINTESTINAL EFFECTS

Several gastrointestinal effects have been examined with regard to a potential relationship to solvent exposure. Pancreatitis occurs when inflammation in and around the pancreas disrupts its exocrine and endocrine functions. Autodigestion (during which digestive enzymes that are normally secreted in an inactive form become activated in the pancreas and begin to digest the pancreatic tissue) is one theory of the pathogenesis of pancreatitis (Greenberger et al., 1998). Chronic pancreatitis is a persistent inflammation that can result in extensive damage. Most of the estimated 50,000–80,000 cases of acute pancreatitis annually in the United States are caused by alcohol abuse or gallstones (NIDDK, 2001). Because chronic alcohol consumption is a known risk factor in the development of pancreatitis, researchers have theorized that occupational-solvent exposure, particularly to alcohol-based solvents, could cause chronic pancreatitis.

Epidemiologic Studies of Gastrointestinal Effects and Exposure to Organic Solvents

There are few epidemiologic data on the potential gastrointestinal effects of exposure to solvents.

Yamaguchi and colleagues (1985; Sato et al., 1987) examined the association between trichloroethylene exposure and pneumatosis cystoides coli, a benign condition of the large intestine involving formation of multiple gas-filled cysts. The cases (n = 13) and

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control subjects (n = 65) in the studies were identified from hospital records in Japan. The study found that 12 of 13 patients with pneumatosis cystoides intestinalis reported trichloroethylene exposure, whereas only five of 65 control subjects reported the exposure ($p < 0.001$). The authors, however, reported almost complete spontaneous disappearance of the condition after discontinuation of exposure to trichloroethylene in several patients who were followed longitudinally, indicating that this condition, although rare, is a short-term consequence of exposure.

Hotz and colleagues (1990) examined the effects of exposure to hydrocarbons in a cross-sectional study of 230 men working in various occupations (such as floor layers or printers). The study included 21 "formerly exposed" workers with a median time since last exposure of 4.2 years (range 0.2–27.9 years). There were no differences in serum amylase and lipase concentrations between men in solvent- or hydrocarbon-related occupations and controls. Serum amylase and lipase concentrations are nonspecific, insensitive measures that can be used in diagnosing pancreatitis. Each of the worker subgroups was small; this, with the healthy-worker effect, could account for the findings.

Concerns about the association between hydrocarbon-related occupations and chronic pancreatitis prompted McNamee and colleagues (1994) to conduct a case–control study in Manchester, England. The occupational exposures of 102 patients who met the diagnostic criteria for chronic pancreatitis were compared with those of 204 age- and sex-matched controls. Two occupational hygienists and two occupational physicians blinded to individual disease status developed a lifetime cumulative hydrocarbon-exposure score from a structured interview and questionnaire. Confounding—attributable to alcohol use, cigarette-smoking, dietary intake of antioxidants, and social class—was considered in the statistical analyses. Increased risks were found to be associated with higher cumulative hydrocarbon exposure scores (OR = 2.67, 90% CI = 1.22–5.87) and lower cumulative exposure (OR = 1.20, 90% CI = 0.61–2.35) after adjustment for a number of factors. For solvent exposures, an increased in pancreatitis was associated with high cumulative exposures to chlorinated solvents (OR = 4.41, 90% CI = 0.69–28.19), but there was a small depression with exposure to paint solvents (OR = 0.87, 90% CI = 0.31–2.52). Because the study was cross-sectional, it is not possible to determine whether the disease developed after an exposure-free period.

Summary and Conclusion

There is little information on the persistent or latent effects of solvent exposure on the gastrointestinal system. The few studies that have examined pancreatic outcomes had inconsistent results and a lack of specific exposure measures.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between exposure to the specific organic solvents under review or solvent mixtures and chronic pancreatitis or other persistent gastrointestinal outcomes.

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RENAL EFFECTS

The kidneys metabolize waste, regulate acid–base concentrations, maintain electrolyte balance, and control fluid levels in the body. That work is accomplished in more than 1 million nephrons, each made up of a glomerulus—a cluster of looping blood vessels in a capsule (Bowman's space)—and a fluid-collecting tubule. Because the glomerulus filters blood, it is particularly susceptible to autoimmune, infectious, metabolic, and chemical insults (including hyperglycemia, mercury, and cadmium) (Brady and Brenner, 1998).

Glomerulonephritis describes a variety of inflammatory conditions in which the glomeruli are damaged and can gradually be destroyed. End-stage renal disease and acute renal failure are possible long-term sequelae. Glomerulonephritis can result from a primary kidney condition or as a manifestation of systemic diseases (such as diabetes), inherited conditions, viral infections (such as hepatitis B or hepatitis C), medication use, or environmental exposures. Most glomerular diseases are immune-mediated and can result in granular or immune complex deposits in the glomeruli. Although most cases of primary glomerulonephritis are related to problems with the immune system, the precise etiology of individual cases can be difficult to identify. In about one-fourth of people with chronic glomerulonephritis, there is no history of kidney disease, and the disorder appears first as chronic renal failure (NLM, 2002).

Epidemiologic Studies of Renal Effects and Exposure to Organic Solvents

A number of studies have examined both the short- and long-term effects on the kidney of exposure to solvents. Acute tubular necrosis has been associated with exposure to a number of solvents. This condition is a reaction to high-dose solvent exposures. It is clinically apparent within a week of exposure. Renal changes are confined to the tubules, and the glomeruli remain intact. The lesions can progress to hemorrhagic cortical necrosis and in some cases to acute or chronic renal failure. Numerous studies have examined markers of glomerular and tubular function associated with solvent exposure, including glomerular filtration rates, 24-hour proteinuria, microalbuminuria, β-2-microglobulin, and *N*-acetyl-β-glucosaminidase (e.g., Brogren et al., 1986; Cai et al., 1991; Krusell et al., 1985; Laitinen et al., 1995; Nagaya et al., 1989; Stevenson et al., 1995). Most studies have been cross-sectional, and they report inconsistent results with various degrees of exposure assessment (Hotz, 1994). Although the committee's primary focus was on epidemiologic studies that used defined health outcomes, these studies of renal function were considered to corroborate the committee's conclusions.

Several case reports associate solvent exposures with Goodpasture's syndrome (autoimmune glomerulonephritis indicated by the production of antiglomerular basement membrane antibodies). In 1972, Beirne and Brennan reported on eight patients with antiglomerular basement membrane antibody-mediated glomerulonephritis from whom extensive exposure histories were obtained by personal interview. The investigators found that six of the eight had extensive exposure to solvents.

One hypothesis regarding the etiology of renal disease has focused on hydrocarbon-related occupational exposures. Several early epidemiologic studies of renal disease reported that occupational exposures to hydrocarbon compounds were higher or more frequent than

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generally seen in control populations (Finn et al., 1980; Lagrue et al., 1976, 1977; Zimmerman et al., 1975). Asal and colleagues (1996) examined hydrocarbons in the development of idiopathic chronic glomerulopathy. The study of 321 matched pairs found an elevated risk for hydrocarbon exposure of 100 ppm or higher (OR = 1.39, 95% CI = 0.94–2.04). A study of Belgian renal patients reported increased risk of chronic renal failure with exposure to oxygenated hydrocarbons (OR = 5.45, 95% CI = 1.84–16.2) on the basis of 25 exposed cases (Nuyts et al., 1995). Yaqoob and colleagues (1992) reported increased risk of primary glomerulonephritis associated with exposure to petroleum products (RR = 15.5, $p < 0.001$), to greasing and degreasing agents (RR = 5.3, $p < 0.01$), and to paints and glue (RR = 2.0, $p < 0.05$) in a case–control study of 55 patients with end-stage renal disease attributed to primary glomerulonephritis. A study by Ravnskov (1986) followed up on patients with glomerulonephritis to examine whether discontinuation of hydrocarbon exposure affected the course of disease. The study reported that patients with subnormal glomerular filtration rates who were no longer exposed to hydrocarbons had a more favorable course than did those who continued to be exposed, despite initially lower mean glomerular filtration rates. Although those studies are informative for this review, the category of "hydrocarbon compounds" often is used more broadly than is "solvents," and it can encompass many non-solvent compounds, including glues, hairsprays, and fuels.

Case–control studies have focused more specifically on solvent exposures. A study in Sweden developed an exposure questionnaire and an exposure measure that also were used by later studies to examine the relationship between renal disease and exposure to solvents (Ravnskov et al., 1979). Ravnskov and colleagues interviewed 50 patients with biopsy-proven glomerulonephritis and 100 sex- and age-matched control subjects (50 patients with nonglomerular renal disease and 50 with acute appendicitis). Solvent exposures were categorized by multiplying the duration of exposure (hours per week multiplied by years of exposure) by an intensity factor (0.5, 1, or 2) determined from the nature of the exposure, the amount of protective equipment used, and the setting. In a discordant-triplet analysis, the point-estimate rate ratio for glomerulonephritis and solvent exposure was 3.9 (95% CI = 1.9–8.1). When the exposure scores were used, there was a trend of increased risk with increased exposure: exposure score less than 1, RR = 1.0; 1–10, RR = 0.6; 11–50, RR = 2.9; and over 50, RR = 4.2 (no other statistical calculations were presented).

Later case–control studies using similar exposure measurement methods reported inconsistent findings. In the Netherlands, van der Laan (1980) identified 50 patients with chronic glomerulonephritis and 50 control subjects from outpatient departments of internal medicine at the same hospitals where the cases were treated. All the cases were newly diagnosed with biopsy. The study reported no differences in solvent exposure between cases and controls (RR = 1.1, 95% CI = 0.4–3.1). The cases in the study were in the early stages of disease, and the group appeared to include fewer highly exposed people than did the group studied by Ravnskov and colleagues (1979).

A study by Franchini and colleagues (1984) reported similar findings. No relationship was found between solvent exposure and chronic glomerulonephritis in comparing the exposures of 116 cases of chronic glomerulonephritis with hospital controls. Solvent exposure was somewhat elevated in the subset of patients with membranous nephropathy.

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As with the preceding studies, a study by Bell and colleagues (1985) assigned a solvent-exposure score based on the responses of 50 patients with biopsy-proven proliferative glomerulonephritis and compared them with the responses of 100 age-, sex-, and social-class-matched controls chosen from acute admissions to two hospitals. The mean solvent-exposure score was greater in the glomerulonephritis group (score = 13,186) than in the control group (score = 3030) ($p < 0.01$).

Occupational and nonoccupational exposures to solvents were examined by Porro and colleagues (1992), who compared 60 patients with biopsy-proven nonsystemic chronic glomerulonephritis and 120 age- and sex-matched control subjects. Comparisons of the exposure scores, estimated in a fashion similar to that used in the preceding studies, revealed a total solvent-exposure score larger in the glomerulonephritis group than in the control group (OR = 3.50, 95% CI = 1.18–12.18). Similar results were reported for the occupational solvent-exposure score (OR = 4.25, 95% CI = 1.18–16.36), but not for the nonoccupational exposure score (OR = 1.71, 95% CI = 0.57–4.94). Logistic regression analyses revealed a trend in occupational-solvent exposure (no exposure, OR = 1.0; lower exposure, OR = 2.12, 95% CI = 0.81–5.57; higher exposure, OR = 5.42, 95% CI: 2.01–14.59; p for linear trend = 0.0002); no similar response to dose was observed for nonoccupational exposures.

Other case–control studies have examined the relationship between glomerular disease and exposure to solvents. Among the largest was a study by Stengel and colleagues (1995) that focused on three subtypes of glomerular nephropathies. Cases (n = 298) were diagnosed at one of five hospitals in France and were age- and sex-matched to 298 controls selected from each hospital. Solvent exposure was assessed with a standard questionnaire; two industrial hygienists grouped responses into five categories of solvents (chlorinated, oxygenated, aromatic, aliphatic, and solvent mixtures) and three intensities of exposure (none, low, and high). Analyses were performed only on male patients (64% of the cases), and the study did not report an association between solvent exposure and glomerulonephritis either at low exposure (OR = 1.0, 95% CI = 0.6–1.6) or at high exposure (OR = 1.2, 95% CI = 0.7–2.1). There were no noteworthy associations between any of the categories of solvents and either all cases of the disease or any of the subtypes. When the investigators divided the cases into those with chronic renal failure and those without, they found that chronic renal failure was associated with high exposures to all solvents (OR = 7.7, 95% CI = 1.4–41.6), as it was for patients with minimal-change nephropathy and for those with IgA nephropathy (OR = 3.5, 95% CI = 1.0–11.8). A linear trend was seen for both end points in an evaluation for duration of exposure (p = 0.03 and p = 0.02, respectively). The detailed analyses could only be performed on small subgroups of the entire study population.

A study in the West Midlands, United Kingdom, enrolled 50 case subjects with glomerulonephritis. The subjects were identified prospectively from people who had renal biopsies (Harrington et al., 1989). Age-, sex-, and ethnic-group-matched controls were selected from within the same practice of the physicians who referred each case. Participants were asked to fill out questionnaires on health and lifetime occupational history. The surveys were assessed in a blinded fashion by an experienced chemist–occupational hygienist. Exposures were categorized as none, low, medium, and high and assigned values of 0, 1, 10, and 100, respectively, for the analysis. The analysis of glomerulonephritis and total solvent exposure (exposed versus nonexposed) found an OR of 1.0 (95% CI = 0.16–6.3). The limitations of this approach include the possibility of overmatching of controls to cases and the arbitrary assignment of values and cutoff points for exposure assessment.

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Sesso and colleagues (1990) investigated rapidly progressive renal failure with biopsy-proven crescentic glomerulonephritis by comparing 17 patients with 34 controls selected at random from patients admitted to the surgical wards of hospitals in Sao Paulo, Brazil. All participants were interviewed by a nurse who was blinded to their status and who used a questionnaire developed by the US National Institute for Occupational Safety and Health that had been translated into Portuguese. Exposures were categorized as "regular" if they included 1 hour or more direct contact per week for at least 3 consecutive months. The RR for rapidly progressive glomerulonephritis with regular exposure to organic solvents was 5.0 (95% CI = 1.14–22.00).

A large, well-designed case–control study that examined the outcome of end-stage renal disease included cases of glomerulonephritis, hypertensive kidney disease, and interstitial kidney disease (Steenland et al., 1990). The investigators identified 325 men with advanced end-stage renal disease from the Michigan Kidney Registry. Control subjects were chosen by using random-digit dialing and matched by age, sex, and residential area. Participants were interviewed over the telephone by persons who were not blinded to case–control status. The information about exposures was reviewed in a blinded fashion by industrial hygienists and then categorized and quantified. When the subjects were analyzed as ever-exposed versus never-exposed, the OR for exposure to all solvents was 1.51 (95% CI = 1.03–2.22). The OR for solvents used in paints and glues was 1.01 (95% CI = 0.58–1.74), for solvents used as cleaning agents or degreasers 2.50 (95% CI = 1.56–3.95), and for solvents used in other processes 1.05 (95% CI = 0.44–2.48). The interviewers' awareness of each subject's case or control status is of concern, but there is no suggestion that they influenced the respondents' recall.

Summary and Conclusion

There has long been interest in exploring the relationship of hydrocarbon exposure and renal disease—with inconsistent results. The relationship between renal disease, particularly glomerulonephritis, and exposure to solvents has been well studied. Animal studies have shown increased tubular cysts and acute tubular degeneration with exposure to toluene, xylene, and other solvents. However, only a few animal studies have reported evidence of glomerular damage (Hotz, 1994). Many of the experimental studies have been conducted with carbon tetrachloride, which is not reviewed in this report.

Most of the human epidemiologic studies used similar methods and a semiquantitative approach to exposure assessment based on self-reporting, which is common in case–control studies (Table 9.4). To overcome the potential for recall bias, many investigators included hospitalized controls. All the studies reviewed included survivors, as opposed to proxies; this can affect results if survivor exposure histories differ from those who have succumbed to chronic renal failure. The results of several case–control studies showed an increased risk of glomerulonephritis with exposure to solvents. One study showed a trend of increased risk with increasing occupational solvent exposure.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between chronic exposure to solvent mixtures and chronic glomerulonephritis.

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TABLE 9.4 Selected Epidemiologic Studies: Renal Disease and Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Glomerulonephritis			
Solvents			
Case–Control Studies			
Ravnskov et al., 1979	Patients in Sweden	50 total cases	3.9 (1.9–8.1)
van der Laan, 1980	Patients in the Netherlands	50 total cases	1.1 (0.4–3.1)
Stengel et al., 1995	Male patients in France	298 total cases	
	Low solvent exposure	21%[a]	1.0 (0.6–1.6)
	High solvent exposure	18%[a]	1.2 (0.7–2.1)
	Chlorinated solvents	4%[a]	0.6 (0.2–1.5)
	Oxygenated solvents	6%[a]	1.2 (0.5–3.0)
	Aliphatics	10%[a]	2.0 (0.9–4.3)
	Aromatics	5%[a]	1.6 (0.5–4.6)
	Solvent mixtures	8%[a]	0.8 (0.4–1.7)
Harrington et al., 1989	Patients in the United Kingdom	50 total cases	1.0 (0.16–6.3)
Sesso et al., 1990	Patients in Brazil	17 total cases	
	Organic solvents	52.9%[a]	5.0 (1.14–22.00)
	Overall hydrocarbons	58.5%[a]	2.8 (0.71–11.07)
Porro et al., 1992	Patients in Italy	60 total cases	
	Total solvent exposures	NA	3.50 (1.18–12.18)
	Occupational	NA	4.25 (1.18–16.36)
	Nonoccupational	NA	1.71 (0.57–4.94)
Hydrocarbons			
Case–Control Studies			
Asal et al., 1996	Patients in Oklahoma		
	Hydrocarbon exposure (<100 ppm vs ≥100 ppm)	132	1.39 (0.94–2.04)
Yaqoob et al., 1992	Patients in the United Kingdom		
	Greasing, degreasing agents	NA	5.3[b] ($p < 0.01$)
End-Stage Renal Disease			
Solvents			
Case–Control Studies			
Steenland et al., 1990	Patients in Michigan		
	All solvents	124	1.51 (1.03–2.22)
	Solvents used in paints and glues	38	1.01 (0.58–1.74)
	Solvents used as cleaning agents or degreasers	94	2.50 (1.56–3.95)
	Solvents used in other processes	17	1.05 (0.44–2.48)
Chronic Renal Failure			
Hydrocarbons			
Case–Control Studies			
Nuyts et al., 1995	Patients in Belgium		
	Oxygenated hydrocarbons	25	5.45 (1.84–16.2)

NOTE: NA = not available.
[a]Percentage of total cases.
[b]Relative risk

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DERMATITIS

Dermatitis is an inflammation of the skin with visible changes that can include scaling, crusting, redness, and swelling. In chronic dermatitis, the skin can remain rough and thickened. There are a number of types of dermatitis, including atopic dermatitis, a cutaneous condition frequently associated with asthma or hay fever. Environmental factors often trigger or exacerbate symptoms of atopic dermatitis. Contact dermatitis is a direct result of exposure to an exogenous compound. Irritant contact dermatitis is a direct toxic effect on the skin that is most often seen on the hands and often can be prevented with skin-protection measures, such as gloves or ointments. A number of compounds—including soaps, cleansers, and harsh chemicals—can cause irritant contact dermatitis, and there is wide variability in individual susceptibility to cutaneous irritants.

Allergic contact dermatitis is a delayed hypersensitivity response that results from an immune reaction to an external substance (Whitmore and Nethercott, 1994). Once sensitivity to a compound is established, exposure to even a small amount can produce a severe reaction (Niland, 1994). Common sensitizers include nickel, fragrances, poison ivy, and preservatives.

Patch testing often is used to distinguish between irritant and allergic contact dermatitis. Diluted antigens (1% for most insecticides) are placed on test strips and applied to the upper back for 48 hours. The patches are read at 48 and 96 hours for evidence of erythema, edema, or vesiculation (Abrams et al., 1991). Patch testing has become highly standardized; the concentrations of the potential allergens are below the irritant threshold, so they do not cause false-positive reactions when applied to the skin of nonsensitized subjects who serve as controls (Adams, 1997; Mathias, 1994).

Epidemiologic Studies of Dermatitis and Exposure to Insecticides

This section reviews the literature on exposure to insecticides and allergic or irritant contact dermatitis. The primary route of human exposure to most pesticides is the skin (Moses, 1989). Although agricultural workers are believed to have a much higher risk of contracting skin disease than workers in industrial occupations, it is difficult to pinpoint the cause of disease from among the many potential agriculture-related exposures, including herbicides, fertilizers, insecticides, and the crop itself (Moses, 1989). The cutaneous hazards of pesticide exposure depend not only on the toxicity of the insecticide formulation but also on the method of application, environmental conditions, the extent of skin protection, and the use of personal-hygiene measures. Reports on the dermatologic effects of insecticide exposure do not always differentiate between irritant and allergic dermatitis and focus primarily on short-term dermatologic outcomes that occur soon after exposure.

Allergic Contact Dermatitis

Dermal-sensitization tests in animals are conducted before insecticide products are registered with the US Environmental Protection Agency, and insecticide labels indicate whether products are potential sensitizers. Several insecticides and insect repellents reviewed in this report have been found to be potentially weak sensitizing agents (such as DEET [*N,N,*-diethyl-3-methylbenzamide], dichlorvos, and malathion), although the sensitizing potential can depend on the formulation (Abrams et al., 1991; Penagos et al.,

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2001). Carbamates and organophosphates in general are not strong irritants or sensitizers (Penagos et al., 2001). The sensitization potential of individual insecticides has been examined in studies of patch testing (e.g., Guo et al., 1996; Sharma and Kaur, 1990).

A cross-sectional study of 122 Taiwanese fruit farmers examined dermal outcomes and skin sensitization (Guo et al., 1996). Skin diseases experienced by the farmers were assessed by a dermatologist through physical examination and questionnaire. Patch tests were conducted on the farmers and on a control group of 63 printing-press workers with no known exposure to pesticides. The farmers reported frequent use of pesticides, including organophosphate insecticides (such as malathion and parathion), pyrethroids, carbamates (such as carbaryl), herbicides, and miticides. Of the 122 farmers, 112 reported that they themselves prepared the pesticides for application; most said they regularly used hats, boots, and masks but not gloves or goggles. That could potentially result in high skin exposure to the frequently used pesticides. Hand dermatitis was exhibited in 30% of the pesticide-exposed subjects (rates of dermatitis in the control group were not provided). It was not possible to determine how long the farmers had experienced dermatitis. Patch testing of a standard series of antigens revealed similar rates of sensitivity to common skin allergens between the groups, and about twice as many farmers (40%) as controls were sensitive to one or more of the pesticides included in the series. One of the farmers had an allergic reaction to malathion as compared with no positive reactions in the controls. Patch testing with carbaryl did not result in positive reactions in farmers or controls.

A study by Sharma and Kaur (1990) examined contact sensitization to 13 insecticides by comparing the patch-testing results of 30 farmers who had previously been treated for contact dermatitis with 20 control subjects. The investigators found that 11 farmers had allergic reactions to one or more of the insecticides, fungicides, or herbicides, including two allergic reactions to malathion, one to carbaryl, and one to lindane. No allergic reactions to dichlorvos were seen. In comparison, there were no allergic reactions in the control subjects. The study is limited by the small number of patch-test participants.

As reviewed by Penagos and colleagues (2001), the literature regarding allergic contact dermatitis and insecticides consists primarily of animal dermal-sensitization data, human case reports, and a few studies of human patch testing generally involving few patients and often lacking an adequate control population. However, the potential for some of the insecticides reviewed in this report to result in sensitization reactions has been demonstrated.

Irritant Contact Dermatitis and Other Skin Disorders

Several studies have looked at dermatitis and occupational exposures; however, the extent to which the studies specifically differentiate between irritant and allergic contact dermatitis varies. A cross-sectional study in the Netherlands studied male agricultural and horticultural workers and pesticide formulators to determine the effects of exposure to various pesticides, including organophosphates, pyrethrins, chlorinated hydrocarbons, carbamates, and fungicides (Ensberg et al., 1974). Attempts were made to estimate the exposure to pesticides on the basis of the type and length of work and the amount of pesticides applied per year (85 workers were in the moderate-to-intensive exposure group, 64 in the slight-to-moderate group). The workers completed a questionnaire and had a physical examination that included blood and urine tests. Control subjects (matched for sex, locality, age, and socioeconomic status) were examined at about the same time. The number

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of subjects with subjective symptoms of dermal sensitivity, itching, or eczema was increased with increased estimated time of exposure. Physical examination confirmed the presence of more skin disease in more highly exposed workers, but patch tests were not performed to differentiate allergic from irritant reactions. The study did not provide details about the effects that were included in the term *skin disease*, and it is not possible to determine how long the dermal effects were present in the workers.

Risk factors for farm-related dermatitis were examined in a cross-sectional study of male farmers in Iowa (n = 382) and the wives of farmers (n = 256), who completed a health and exposure questionnaire (Park et al., 2001). Among the men, the risk of dermatitis during the previous year was not increased with application of insecticides on field crops (OR = 0.63, 95% CI = 0.25–1.56) or with application of insecticides to livestock (OR = 1.29, 95% CI = 0.66–2.50). A history of allergy was the only risk factor meaningfully associated with dermatitis. The study was population-based, but the authors acknowledge a low response rate.

Gamsky and colleagues (1992) studied dermatitis in California farm workers and compared grape, citrus, and tomato workers. The study identified a wide array of pesticides used, including elemental sulfur in the vineyards. Grape workers experienced the highest prevalence of dermatitis, but their exposures were not well characterized, and there were many possible confounders. Other studies have examined dermatologic effects of pesticides with similar problems of multiple confounders and poorly characterized exposure (Cellini and Offidani, 1994; Cole et al., 1997; Matsushita et al., 1980).

One study of Gulf War veterans examined the potential dermatologic effects of pesticide exposure during the war in concert with other symptoms and exposures. Proctor and colleagues (1998) studied the symptom experience of a stratified random sample of two cohorts of Gulf War veterans from Massachusetts (Ft. Devens) (n = 220) and New Orleans (n = 71), both consisting of active-duty, reserve, and National Guard troops deployed to the Gulf War area. The control group (n = 50) consisted of veterans who had been deployed to Germany during the Gulf War. Subjects completed symptom checklists, exposure questionnaires, other tests, and interviews. The greatest differences between case subjects and the control group were in dermatologic symptoms (such as skin rash, eczema, and skin allergy), neuropsychologic symptoms (such as difficulty in concentrating and in learning new material), and gastrointestinal symptoms (such as stomach cramps and excessive gas). With multiple regression and adjustment for other exposures, pesticide exposure was associated with neurologic symptoms and musculoskeletal symptoms but was not found to be related to dermatologic, gastrointestinal, neuropsychologic, or psychologic symptoms.

Summary and Conclusion

Many of the studies on dermatitis and insecticide exposure examined workers with continuing exposures to insecticides, so it is not possible to determine whether the dermatitis was a short- or long-term health effect of insecticide exposure. In addition, those studies examined agricultural workers who experienced multiple confounding exposures that are not always subject to control. Although case studies and review articles discuss an increased incidence of short-term dermatitis after handling pesticides, there is a limited amount of information about the long-term dermatologic effects of insecticide exposure. Several of the insecticides reviewed in this report have been found to be potential sensitizers, and reexposure to those agents could result in allergic contact dermatitis in sensitized persons.

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However, there are few epidemiologic studies of exposure to insecticides and allergic contact dermatitis, and studies conducted to date have focused on a variety of insecticides and have involved small study populations.

The committee concludes, from its assessment of the epidemiologic literature, that there is limited/suggestive evidence of an association between exposure to some of the insecticides under review and allergic contact dermatitis that results from sensitization to the compounds and subsequent reexposure.

There is inadequate/insufficient evidence to determine whether an association exists between exposure to the insecticides under review and chronic irritant contact dermatitis after cessation of exposure.

Epidemiologic Studies of Dermatitis and Exposure to Organic Solvents

Many solvents are irritants to the skin and cause acute dermatitis. Solvents alter the chemical and physical barriers of the epidermis, remove the lipid film on the surface and thus diminish the protective capacity of the skin. Acute dermatitis can occur after a single exposure or as a cumulative effect after repeated insults by low-grade irritants over a long period. Dryness and cracking of the skin are often the initial features of irritant contact dermatitis with redness, scaling, papules, vesicles and a gradual thickening of the skin developing over time. Irritant contact dermatitis can persist if untreated soon after the initial appearance. Even when the dermatitis appears to be healed, the protective capacity of the skin is still impaired for a period (Andersen, 1986).

Allergic Contact Dermatitis

Numerous case reports and case series have been included in the medical literature regarding allergic contact dermatitis and exposure to propylene glycol, a solvent widely used in foods, drugs, and cosmetics. Patch testing, used to confirm the diagnosis of allergic contact dermatitis, may have positive results for only a fraction of study participants because not everyone is sensitized to the compound. It has been noted that, because many solvents are irritants, it is difficult to test their potential for allerginicity with standard patch-test techniques (Wahlberg and Adams, 1999).

Using 100% propylene glycol, Andersen and Storrs (1982) patch-tested 84 dermatitis patients and reported that five of 12 patch-test-positive patients had allergic reactions; seven had irritant reactions. In followup tests, 248 eczema patients were patch-tested with propylene glycol at 100%, 20%, and 2% concentrations. Two of five patients with positive reactions to the patch tests developed an eczematous eruption after oral provocation with 15 mL of propylene glycol, confirming its potential as a sensitizer. The authors state that positive patch test reactions to propylene glycol are difficult to interpret and that allergic reactions can be confirmed by clinical relevance, repeated local skin provocation, or oral provocation.

Angelini and Meneghini (1981) conducted patch testing on 400 subjects with 20% propylene glycol in water and six of them developed an allergic contact dermatitis. Hannuksela and colleagues (1975) subjected 1556 eczema patients to a chamber test with propylene glycol, ethylene glycol, and polyethylene glycol. They reported 12.5% positive

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reactions to propylene glycol, 30% of which were allergic in appearance. Not all studies determined a diagnosis of allergic contact dermatitis with exposure to propylene glycol. For example, at a skin clinic, Nater and colleagues (1977) conducted patch tests on 98 outpatients with eczema with propylene glycol. Eleven had positive patch-test reactions after a 48-hour application. However, because none of the study's subjects gave a history consistent with possible allergic contact dermatitis related to propylene glycol, the authors concluded that all the reactions were irritant effects.

Wolf and colleagues (1994, 1996) evaluated the hand dermatitis of Israeli soldiers with occupational dermatitis. Cases and controls were patch-tested with a standard battery of contact sensitizers and five additional reagents: gun oil, hydraulic oil, automotive lubricant oil, white spirits, and gasoline. Olive oil was used as a control. In the exposed group, 31 patients (29%) had at least one positive skin reaction to the oil series, and 30 had reactions to the standard patch-test arrays. None of the 20 soldiers exposed to fuels and oils, but without dermatitis, had a positive test in the oil series. This study provides some indication that exposure to some oils, white spirits, and fuels can result in allergic contact dermatitis. However, no data are provided about clearing of the dermatitis after cessation of exposure.

Irritant Contact Dermatitis and Other Skin Disorders

Many of the studies of contact dermatitis involve workers who continue to be exposed to the substances of concern, so it is difficult to determine long-term effects after exposure ceases. Several descriptive studies reported a high prevalence of skin problems, including dermatitis, in workers exposed to solvents (e.g., Atav and Spencer, 1995; Cherry et al., 2000; Goon and Goh, 2000). However, those studies did not have control groups for comparison.

Yakes and colleagues (1991) conducted a cross-sectional study of newspaper pressroom workers. They obtained responses to a comprehensive health questionnaire and performed a skin examination of 212 pressroom workers. The results were compared with results in 33 compositors. On the questionnaire, pressroom workers were more likely to complain of dryness or cracked skin, itching, acne, and redness than were compositors (p values were all < 0.05). Dermatitis was correlated with more frequent use of type 1 solvent (mineral spirits and naphtha blend), Cleansall (aliphatic hydrocarbons, pine oil, and surfactants), and isopropyl alcohol (p values were all < 0.05). Participation rates in the study were high (over 90%), but only continuous exposure and disease were measured.

Svendsen and Hilt (1997) compared skin disorders in ships' engineers exposed to mineral oil and solvents in the engine room with disorders in other seamen. On a questionnaire, engineers were more likely than were control subjects to report eczema, acne, dry skin, and any dermatitis. Use of Stoddard solvent was found to be positively associated with acne (OR = 2.2, 95% CI = 0.86–5.46), and there was a weaker association with hand dermatitis (OR = 1.1, 95% CI = 0.60–2.11).

Burg and Gist (1999) analyzed data from the trichloroethylene subregistry of the Agency for Toxic Substances and Disease Registry (ATSDR). Registrants were exposed to trichloroethylene-contaminated water and also might have been exposed to trichloroethane, tetrachloroethylene, dichloroethane, and dichloroethene. The study categorized the 4041 living members on the registry into four groups by amount and duration of exposure and examined the groups for possible relationships with 25 health outcomes. Using a cumulative trichloroethylene exposure index of parts-per-billion–years (ppb-yr) adjusted for age and

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sex, risks for skin rashes were estimated (in comparison to the 0-49 ppb-yr group) for exposures of 50–499 ppb-yr (OR = 1.02), 500–4999 ppb-yr (OR = 1.29), and 5000 or more ppb-yr (OR = 1.20), which all had confidence intervals overlapping 1.0. This study uses the term *skin rashes* to include rashes, eczema, and other skin allergies. In addition to bias associated with health outcomes being self-reported, bias might arise from the self-selection of people choosing to be enrolled in a registry. The use of the lowest exposure category as the referent group could bias the risk estimates towards the null, since these subjects might be experiencing some level of response greater than that of a strictly unexposed control group.

Health effects in semiconductor-industry workers were examined by McCurdy and colleagues (1995), who performed a cross-sectional survey of workers in eight locations. Participants reported outcomes on a questionnaire, and the responses were analyzed by comparing fabrication workers with nonfabrication workers; fabrication workers were subdivided into work groups. Reporting dermatitis within the preceding year was more common in fabrication workers than in nonfabrication workers (OR = 1.19, 95% CI = 1.04–1.35). The authors reported a weak relationship between dermatitis and intensity of exposure to methanol and isopropanol, with RRs in the highest-exposure categories for those solvents of 1.37 (95% CI = 1.08–1.70) and 1.24 (95% CI = 1.02–1.48), respectively. Limitations of this study include multiple continuous exposures associated with the outcomes of interest.

Summary and Conclusion

Many solvents are skin irritants. Irritant contact dermatitis is evident soon after exposure, but usually dissipates within a short time of removal of the irritant. In some cases, however, irritation might persist for months, or rarely longer, after exposure ceases.

Because allergic contact dermatitis results from sensitization to an external substance, the underlying sensitization to the allergens can persist indefinitely after the exposure has ceased. As discussed above, there are a number of case reports and some epidemiologic evidence that propylene glycol is an allergic sensitizer. Those sensitized to the compound may experience allergic contact dermatitis on reexposure to the sensitizing agent.

The committee concludes, from its assessment of the epidemiologic literature, that there is sufficient evidence of an association between exposure to propylene glycol and allergic contact dermatitis that results from sensitization to the compound and subsequent reexposure.

MULTIPLE CHEMICAL SENSITIVITY

Multiple chemical sensitivity (MCS)[5] is a controversial condition marked by sensitivity to low chemical exposures. It is not formally recognized in *ICD-10 (International Classification of Diseases*, 10th revision) or by major medical associations as a discrete syndrome. Research criteria for MCS often specify symptoms of fatigue, cognitive impairment, respiratory inflammation, headaches, and other symptoms. The etiology of MCS is unknown, but may involve neuronal sensitization of mesolimbic pathways after

[5]Also called idiopathic environmental intolerances.

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chemical exposure (Graveling et al., 1999). Because symptoms associated with MCS are frequently reported by Gulf War veterans, researchers have sought to establish whether veterans meet research criteria for MCS and whether self-reported insecticide or solvent exposures during the Gulf War are associated with onset.

For the purposes of this report, the committee sought to evaluate studies related to MCS that examined populations with known exposure to the relevant insecticides or organic solvents. Furthermore, studies were sought that evaluated participants (compared with a control or comparison group) after an exposure-free interval to identify long-term, rather than short-term, effects. The committee was not able to identify any occupational studies that met those criteria. Several studies of Gulf War veterans and MCS are described below. However, there is not a sufficient body of epidemiologic evidence with information on exposure to the relevant insecticides or solvents to support conclusions on this outcome.

Three studies addressed the possibility of an association between MCS and pesticide exposures during the Gulf War. They varied widely in their methods, samples of veterans, and definitions of exposures and of MCS. In the most methodologically rigorous of the three studies, Reid and colleagues (2001) further analyzed a population-based, random sample of British Gulf War veterans assembled by Unwin and colleagues (1999). MCS cases were defined by criteria used by Simon and colleagues (1993). The criteria required self-reported symptoms for at least 3 months related to at least three organ systems (including the central nervous system) and sensitivity to four or more of 11 substances that were included in the Unwin exposure questionnaire (the Simon criteria had a list of 14). Reid and colleagues (2001) set aside the two comparison cohorts developed by Unwin and colleagues (1999), thus restricting their analysis to responses from the Gulf War veteran cohort. About 1% of the Gulf War cohort matched the Simon criteria for MCS, and 0.8% indicated that they thought they had MCS. But there was little overlap between the two groups. Veterans who met the MCS criteria were much more likely (OR = 14.6, 95% CI = 7.2–26.6) to meet criteria for posttraumatic stress disorder (PTSD). Exposures to any of 23 Gulf War exposures were compared in veterans who met the MCS criteria and those who did not; the researchers used a logistic regression analysis that adjusted for sex, age, marital status, education, rank, and employment status at followup. The risk estimates of criteria-defined MCS were increased for most of the chemical exposures. For "personal pesticides" (OR = 10.9, 95% CI = 2.6–45.8) and "pesticides on clothing or bedding" (OR = 12.3, 95% CI = 5.1–30.0), the estimated risks were the highest found in the study. The adjusted OR for "POW exposure" (which could involve exposure to lindane, a delousing agent) was 4.0 (95% CI = 1.8–8.9). The authors concluded that, "the relationship between MCS and pesticide exposure deserves further exploration." The limitations of the study were self-reported symptoms and exposures and the potential for recall bias.

In the second study on Gulf War veterans, Bell and colleagues (1998) compared rates of self-perceived chemical intolerance in random samples of deployed and nondeployed veterans from the Tucson Veterans Affairs Medical Center and reported on perceived exposures to chemical agents during the Gulf War. A 15-minute telephone interview collected data on the veterans' self-perceptions of their health (at the time of the interview, 6 months before, and just before entering and after leaving military service), plus self-reports of the diagnosis of PTSD and of intolerance to chemical odors of 17 substances. Self-reports regarding six exposures in the Gulf War were also solicited, and degree of exposure to each agent was rated on a 10-point scale. From an initial random sample of 100

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veterans, the investigators contacted 28 Gulf War and 20 Gulf War era veterans (military personnel who were not deployed to the Gulf War but served during the same time period); 24 Gulf War and 17 Gulf War era veterans agreed to participate. Female veterans were oversampled in both groups because of early reports of higher rates of chemical sensitivity in women. For purposes of analysis, Gulf War veterans were first dichotomized into "healthy" and "ill" on the basis of changes in their self-reports of health status between the time preceding enlistment and the time of the survey. Veterans designated as "ill" in this analysis were further dichotomized into groups with and without deterioration in their tolerance to chemical odors since entry into the service. The comparison of ill and healthy Gulf War veterans resulted in ORs of 5.6 (95% CI = 0.81–38.5) for pesticide exposure and 5.5 (95% CI = 0.91–33.2) for insect-repellent exposure. Although not statistically precise, the risk estimates for associations with pesticide exposure were larger than those for other exposures. When ill Gulf War veterans whose self-perception of chemical sensitivity had increased since deployment were compared with healthy veterans, the associations with exposure to both pesticides (OR = 12, 95% CI = 1.3–111.3) and insect repellents (OR = 12, 95% CI = 1.1–136.8) were elevated. The researchers considered the findings preliminary. The study's limitations included a nonrepresentative sample drawn from the patient population of the Veterans Affairs Medical Center and self-reported exposures and symptoms.

In the third study of MCS, Miller and Prihoda (1999) recruited a group of 72 Gulf War veterans with advertisements in MCS patient-group newsletters and word of mouth. No attempt was made to identify individual veterans who met the criteria for MCS, but the sample of veterans obtained had symptoms and symptom severity scores that were comparable with those of patients with MCS who were included in the same study. No attempt was made to determine actual exposures, but veterans were asked to identify exposures that they thought had led to their symptoms. Of the Gulf War veterans, two (3%) identified pesticide exposure during the Gulf War as a cause of their symptoms. However, this study is limited by the self-selected nature of the veteran sample and was not constructed to test hypotheses of causality.

Summary

Only one of the studies addressing MCS in Gulf War veterans can be considered a high-quality study. It is notable for its rigorous methods, random sample of British Gulf War veterans, and use of a definition of MCS that had been used in earlier studies; but there did not seem to be a unique association between pesticides and MCS, inasmuch as most of the exposures assessed resulted in positive associations with the symptom criteria for MCS. A second study used a very small, and possibly nonrepresentative, sample; and a third used a nonrepresentative sample and made no attempts to assess actual exposures. All three studies used self-reports of exposures, raising the possibility of recall bias. Because of the lack of other epidemiologic studies of MCS specifically addressing solvent or insecticide exposure, the committee did not form a conclusion on this outcome. Of course, studies of MCS necessarily examine exposure to a multiplicity of chemicals.

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SYSTEMIC RHEUMATIC DISEASES

Epidemiologic Studies of Exposure to Organic Solvents

Scleroderma

Scleroderma encompasses disorders that involve abnormal growth of connective tissue resulting in a variety of clinical manifestations, from thickening and tightening skin to problems with blood vessels or internal organs. Although the etiology of the disease is not known, it is thought to be an autoimmune disease in which stimulated fibroblast cells produce excess collagen. Systemic scleroderma, or systemic sclerosis, is estimated to affect 40,000–165,000 people in the United States, with a female-to-male ratio of 3:1 (Medsger, 1994; NIAMS, 2001). Research suggests that environmental exposure (such as to viral infections and some adhesives) can trigger scleroderma in people who are genetically predisposed (NIAMS, 2001).

Several studies have examined the relationship between solvent exposure and scleroderma. Scleroderma is a rare disease, and most studies involve small numbers of cases. Lundberg and colleagues (1994) conducted a population-based study of 375,035 men and 140,139 women in Sweden, using census data linked to hospital-discharge data. In all, 47 men and 24 women had been treated for systemic sclerosis. By using a job–exposure matrix, they categorized occupations as exposed or not exposed to several chemicals. The study found an increased association for systemic sclerosis in men exposed to aliphatic hydrocarbons (RR = 2.1, 95% CI = 0.8–5.5). Risk estimates for systemic sclerosis and solvent exposure in women were not reported.

In a case–control study of male scleroderma patients in the United Kingdom, Silman and Jones (1992) mailed questionnaires about occupational exposures to the 56 case patients, 56 control subjects referred by the patients' physicians, and 41 control subjects who were friends of the patients. Job descriptions and histories were blinded and assessed by an occupational hygienist. The study revealed positive associations for self-reported exposure to organic solvents when 18 exposed cases were compared with the physicians' controls (OR = 1.7, 95% CI = 0.7–4.1) or with friend controls (OR = 2.3, 95% CI = 0.9–6.2). Duration of exposure (none, 0–9 years, 10–19 years, 20 years or more) did not correlate with a trend of increasing risk in comparison with either control group.

Nietert and colleagues conducted two studies (1998, 1999) of 178 systemic sclerosis patients at a rheumatology clinic in South Carolina. They assigned 200 control subjects with other rheumatologic diseases from the same referral practice. All participants were interviewed to determine residential, occupational, and medical histories. Laboratory tests were used to determine the presence of Scl70 autoantibodies, which are associated with some types of the disease. The 1998 study focused on occupational exposures to solvents and used a job–exposure matrix to categorize occupational histories by intensity of exposure (none, low, medium, or high). That study reported increased risk of systemic sclerosis for males with high cumulative intensity of "any solvent exposure" (OR = 2.9, 95% CI = 1.1–7.6; 60 exposed cases), maximal intensity of "any solvent exposure" (OR = 2.9, 95% CI = 1.2–7.1; 57 exposed cases), or maximal intensity of exposure to trichloroethylene (OR = 3.3, 95% CI = 1.0–10.3). No such positive associations were found for men in relation to exposure to benzene, carbon tetrachloride, and trichloroethane or for females with respect to

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any intensity of solvent exposure or exposure to the four specific solvents. This study adjusted only for age at onset of disease.

Another study of this population examined exposure to solvents through hobbies (Nietert et al., 1999). The study found that the association between systemic sclerosis and solvent exposure from hobbies was only moderately increased for the group as a whole (OR = 1.1, 95% CI = 0.7–1.9). High cumulative solvent-oriented hobby exposure was greater in patients who were positive for the blood test Scl70 than for those with negative test results (OR = 2.9, 95% CI = 1.1–7.9), and it was greater when compared with controls (OR = 2.5, 95% CI = 1.1–5.9). The study design did control for potential confounders, including age at disease onset, sex, and intensity of occupational exposure.

Bovenzi and colleagues (1995) conducted a small case–control study in Trento, Italy, that interviewed 21 case subjects with scleroderma and 42 age- and sex-matched referents identified from hospital records. On the basis of only four cases exposed to solvents, the study reported an OR of 9.28 (95% CI = 1.08–243.8).

Goldman (1996) conducted a questionnaire survey of patients in a rheumatology practice and reported an increase in exposure to organic solvents in a subset of patients with scleroderma (12 of 33 scleroderma patients) compared with patients with other rheumatologic diseases (22 of 246 patients, $p = 0.00001$). However, the survey did not control for potentially confounding exposures.

Czirjak and colleagues (1989) reported that 28% of 61 patients with systemic sclerosis had prior exposure to chemicals, primarily solvents. The study did not, however, report the exposure rate in the control group.

Other Rheumatologic Diseases

A few epidemiologic studies have been conducted on other rheumatologic diseases in connection with exposure to solvents. Kilburn and Warshaw (1992) studied patients with systemic lupus erythematosus (SLE), a chronic inflammatory disease of unknown etiology. A group of 362 residents of Tucson, Arizona, had laboratory tests and participated in occupational- and medical-history interviews. The group was identified as possibly having been exposed to water contaminated with trichloroethylene, trichloroethane, inorganic chromium, and other substances. A group of 158 Phoenix residents served as a regional comparison population. SLE symptoms were reported considerably more often by the exposed group. Blood tests showed increased concentrations of antinuclear antibodies (associated with SLE) more often in females in the exposed group than in the comparison population, but notable differences were not seen in blood-test results of exposed and control males.

Rheumatoid arthritis was the primary focus of a large population-based study (described above) by Lundberg and colleagues (1994). By linking Swedish census data and hospital-discharge data, the study identified 896 males and 629 females who had been treated for rheumatoid arthritis in 1981–1983. The study reported an increased risk of rheumatoid arthritis in male spray painters and lacquer workers (RR = 2.4, 95% CI = 1.1–5.4). Female launderers and dry-cleaning workers had an increased relative risk on the basis of seven cases. In the analysis, which was based on a job–exposure matrix of occupational use of solvents, the study reported an increase for males with substantial use of organic solvents (RR = 1.2, 95% CI = 1.0–1.6), but the results for women in the same exposure category did not suggest increased risk (RR = 0.9, 95% CI = 0.3–2.8), although there were

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only four exposed cases. The authors noted that there were only small differences in the risk of rheumatoid arthritis among the different occupations. The jobs studied often involved manual labor. It is possible that people with rheumatoid arthritis are less likely to seek such jobs (because of pain or deformity of their hands) and that the study therefore underestimated the association. Conversely, it is possible that rheumatoid arthritis was more likely to be diagnosed in people whose work required the use of their hands and that the study therefore overestimated the association.

Undifferentiated connective-tissue disorder (UCTD) is the term used to describe a condition with nonspecific rheumatic symptoms that do not meet the criteria for any specific rheumatic disease. Lacey and colleagues (1999) conducted a case–control study involving 205 females with UCTD, compared with 2095 population-based female control subjects identified by random-digit dialing. Interviews were conducted to assess occupational exposures to solvent-containing products and to specific solvents. The study reported an elevated risk of UCTD with painting or paint manufacturing (OR = 2.87, 95% CI = 1.06–7.76) and with some solvents and solvent products. Of 32 patients reporting exposure to paint thinners or paint removers, the OR was 2.73 (95% CI = 1.80–4.16). For 18 patients exposed to mineral spirits, naphtha, or white spirits, the OR was 1.81 (95% CI = 1.09–3.02). Analyses for trichloroethylene, toluene, and other specific solvents involved few exposed cases and did not show consistent increases in risk. Control for confounding included adjustments for age at diagnosis and year of birth. The study was subject to strong recall bias.

Summary and Conclusion

The studies reviewed by the committee have reported inconsistent results for an association between systemic rheumatic diseases and exposure to solvents (Table 9.5). As with studies of other health effects, the exposures lack specificity and their assessments involve the use of job categories with wide variations in exposure. Although there is an indication of elevated risks in several studies of scleroderma and exposure to solvents, additional studies using control groups could clarify the nature of this association.

The committee concludes, from its assessment of the epidemiologic literature, that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to specific organic solvents under review or solvent mixtures and the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus.

TABLE 9.5 Selected Epidemiologic Studies: Systemic Rheumatic Diseases and Exposure to Organic Solvents

Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Scleroderma			
Case–Control Studies			
Lundberg et al., 1994	Swedish residents with systemic sclerosis		
	Aliphatic hydrocarbon exposure	6	2.1 (0.8–5.5)
Silman et al., 1992	Scleroderma cases in the United Kingdom	18	
	Organic solvent exposure		
	Compared with general practitioner controls		1.7 (0.7–4.1)
	Compared with friend controls		2.3 (0.9–6.2)

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Reference	Population	Exposed Cases	Estimated Relative Risk (95% CI)
Nietert et al., 1998	Systemic sclerosis patients in South Carolina, occupational exposure		
	Males		
	Solvents, maximal intensity	57	2.9 (1.2–7.1)
	Trichloroethylene, maximal intensity	10	3.3 (1.0–10.3)
	Females		
	Solvents, maximal intensity	4	0.6 (0.2–1.9)
	Trichloroethylene, maximal intensity	6	0.9 (0.3–2.3)
Nietert et al., 1999	Systemic sclerosis patients in South Carolina, hobby exposure	178	1.1 (0.7–1.9)
Bovenzi et al., 1995	Occupational exposures in scleroderma cases, Trento, Italy	4	9.28 (1.08–243.8)
Rheumatoid arthritis			
Case–Control Studies			
Lundberg et al., 1994	Swedish registry cases of rheumatoid arthritis		
	Males		
	Substantial use of organic solvents	68	1.2 (1.0–1.6)
	Spray painters and lacquer workers	6	2.4 (1.1–5.4)
	Females		
	Substantial use of organic solvents	4	0.9 (0.3–2.8)
	Launderers and dry-cleaning workers	7	1.5 (0.7–3.2)
Undifferentiated connective-tissue disorder			
Case–Control Studies			
Lacey et al., 1999	Cases of undifferentiated connective-tissue disorder		
	Painting or paint manufacturing	5	2.87 (1.06–7.76)
	Paint thinners or removers	32	2.73 (1.80–4.16)
	Mineral spirits, naphtha, white spirits	18	1.81 (1.09–3.02)

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APPENDICES

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A

OVERVIEW OF ILLNESSES IN GULF WAR VETERANS

Miriam Davis, PhD[1]

A decade after the Gulf War, questions persist about illnesses reported by veterans. About 20% of Gulf War-deployed veterans receive some form of disability compensation.[2] A sizable number of veterans report having fatigue, rash, headache, muscle and joint pain, and loss of memory (Joseph, 1997; Murphy et al., 1999). An increased prevalence of those symptoms has been borne out by large controlled studies of deployed and nondeployed military personnel[3] from four countries—the United States, the United Kingdom, Denmark, and Canada. That so many Gulf War veterans report unexplained[4] symptoms and disability has prompted concerns about their exposure to potentially hazardous agents during the Gulf War. The US government has invested substantially in health research to understand veterans' illnesses, search for their causes, and find effective treatments (CDC, 1999; IOM, 2001; Research Working Group, 1999).

This appendix describes the research that has addressed three fundamental questions about illnesses in Gulf War veterans:[5] What are the nature and prevalence of veterans' symptoms and illnesses? Do their unexplained symptoms warrant classification as a new syndrome? Are exposures to specific biologic, chemical, and radiologic agents during the Gulf War associated with veterans' symptoms and illnesses? Those questions are designed to guide the reader through a complex body of research. The appendix summarizes studies of Gulf War veterans' symptoms, diagnosable illnesses, mortality, and hospitalizations; and it provides a brief overview of the Gulf War veterans registry programs established by the Department of Veterans Affairs (VA) and the Department of Defense (DOD). The

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[2]About 155,000 of the more than 700,000 Gulf War veterans receive various degrees of disability compensation or a disability pension from the Department of Veterans Affairs (Sullivan, P, personal communication, Dec. 14, 2001).

[3]Many studies have compared the health of military personnel deployed to the Gulf War with that of military personnel who were not deployed to the Gulf War but served during the same period (Gulf War era). Some studies have a comparison cohort of military personnel who served in another deployment (such as Bosnia).

[4]*Unexplained symptoms* or *unexplained illnesses* mean that health complaints cannot be accounted for or explained by current medical diagnoses.

[5]This appendix uses the term *Gulf War veterans* in the broadest sense. Unless otherwise specified, the term denotes all military personnel who served in the Gulf War theater between August 2, 1990, and June 13, 1991, regardless of whether they later continued on active duty, returned to the reserves or National Guard, or left military service.

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information presented here offers background for the reader and offers context for members of the IOM committee.

This appendix updates a previous chapter on Gulf War illnesses contained in the first volume (IOM, 2000). Some studies of Gulf War veterans covered here are also discussed more thoroughly in the body of this volume because they are relevant to understanding the health effects of insecticides and solvents. There, they are incorporated into the body of evidence evaluated by the committee to reach its conclusions about the health effects of insecticides and solvents.

REGISTRY PROGRAMS

Some 700,000 US servicemen and servicewomen were deployed in the Gulf War in 1990 and 1991 (PAC, 1996). The demographic composition of the deployment was more diverse than that of previous deployments; there were greater racial and ethnic diversity, more women, and more reserves and National Guard troops (Table A.1).

TABLE A.1 Demographic Characteristics of US Gulf War Troops

Characteristic	Percentage of Troops[a]
Sex	
Male	93
Female	7
Age (mean) in 1991 (years)	27
Race or ethnicity	
Non-Hispanic/White	70
Black	23
Hispanic	5
Other	2
Rank	
Enlisted	90
Officer	10
Military branch	
Army	50
Navy	23
Marines	15
Air Force	12
Military Status	
Active DutyReserves or	83
National Guard	17

SOURCE: Joseph, 1997

[a]Total about 697,000 US military personnel.

Soon after the war ended in 1991, veterans began to seek medical treatment for a variety of symptoms and illnesses (PAC, 1996). DOD and VA responded to veterans' health concerns by establishing programs for veterans to voluntarily receive clinical examinations largely for diagnostic purposes. By 1994, those registry programs had been revised and renamed the Comprehensive Clinical Evaluation Program (hereinafter called the DOD registry) and the Persian Gulf Registry and Uniform Case Assessment Protocol (hereinafter called the VA registry). The programs are similarly structured. They begin with an initial physical examination, including patient and exposure history and screening laboratory tests, which are followed by an opportunity for referral to more-specialized testing and

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consultation if needed (Joseph, 1997; Murphy et al., 1999).[6] About 125,000 Gulf War veterans underwent registry health examinations through March 1999 (IOM, 1999a), most conducted under VA auspices. The programs continue to register participants.

The symptoms most commonly reported in 1992–1997 by the 52,835 participants in the VA registry were fatigue, rash, headache, muscle and joint pain, and loss of memory (Table A.2) (Murphy et al., 1999). An almost identical set of symptoms was reported most frequently among the roughly 20,000 participants in the DOD registry (CDC, 1999). Veterans classified in the DOD registry as having "symptoms, signs, and ill-defined conditions" complained most frequently of fatigue, headache, and memory loss (Roy et al., 1998). Clinicians were able to arrive at a primary diagnosis for about 82% of symptomatic DOD registry participants (Joseph, 1997) and for a similar fraction of VA registry participants (Murphy et al., 1999) (Table A.2).

TABLE A.2 Most Frequent Symptoms and Diagnoses 53,835 Participants in VA Registry (1992–1997).

Symptoms or Diagnoses	Frequency, %
Self-Reported Symptoms	
Fatigue	20.5
Skin rash	18.4
Headache	18.0
Muscle and joint pain	16.8
Loss of memory	14.0
Shortness of breath	7.9
Sleep disturbances	5.9
Diarrhea and other gastrointestinal symptoms	4.6
Other symptoms involving skin	3.6
Chest pain	3.5
No complaint	12.3
Diagnosis (ICD-9-CM)	
No medical diagnosis	26.8
Musculoskeletal and connective tissue	25.4
Mental disorders	14.7
Respiratory system	14.0
Skin and subcutaneous tissue	13.4
Digestive system	11.1
Nervous system	8.0
Infectious diseases	7.1
Circulatory system	6.4
Injury and poisoning	5.3
Genitourinary system	3.0
Neoplasm	0.4

SOURCE: Murphy et al., 1999.

A registry program established by the United Kingdom Ministry of Defence for UK Gulf War veterans found similar types and frequencies of symptoms and diagnoses (Coker et al., 1999). The most recent publication from the British registry found 20% to be unwell, predominantly with psychiatric diagnoses, especially posttraumatic stress disorder (Lee et al., 2001). Across the registries, musculoskeletal disease; mental disorder; and symptoms, signs, and ill-defined conditions[7] were the three most common diagnostic categories,

[6]Several independent advisory committees have reviewed these programs and made recommendations for their refinement (NIH, 1994; IOM, 1995, 1996, 1997, 1998; PAC, 1996).

[7]"Symptoms, signs, and ill-defined conditions" refers to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 780–799, which are reserved for 160 subclassifications of ill-defined common conditions not coded elsewhere in ICD-9-CM or lacking distinct physiologic or psychologic basis (US DHHS, 1998).

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together accounting for more than 50% of primary diagnoses (CDC, 1999). Registries are self-selected case series of veterans who presented for care, so they cannot and were not intended to be representative of the symptoms and illnesses of the entire group of Gulf War veterans. Nor were registries designed with control groups or with diagnostic standardization across the multiple sites at which examinations took place (Joseph, 1997; Roy et al., 1998). Finally, owing to their reliance on standard diagnostic classifications, registries were not designed to probe for novel diagnoses[8] or to search for biologic correlates. Thus, because of their methodologic limitations, registry studies cannot stand alone as a basis of conclusions or of the conduct of research.

Registry programs, do, however, provide a glimpse into veterans' symptoms and the difficulties of fitting them into standard diagnoses. Registry programs are a valuable source of information for generating hypotheses. The hypotheses can be tested in rigorous epidemiologic studies with control groups to estimate the population prevalences of symptoms among Gulf War veterans and compare them to rates among otherwise similar troops who were not deployed to the Gulf War.

EPIDEMIOLOGIC STUDIES OF VETERANS' SYMPTOMS AND GENERAL HEALTH STATUS

A number of epidemiologic studies have been conducted on the health status of Gulf War veterans. The driving issues behind many of the studies have been to determine the nature of symptoms and symptom clusters, whether symptom clusters constitute a new and unique syndrome, and what types of exposures might have produced the symptoms. The second issue—the quest to define a new syndrome—requires some explanation. The question is whether unexplained symptoms constitute a syndrome and, if so, whether they are best studied and treated as a unique, new syndrome or a variant form of a known syndrome (IOM, 2000). The finding of a new set of unexplained symptoms in a group of patients does not automatically mean that a new syndrome has been found. Rather, it constitutes the beginning of a process to demonstrate that the patients are affected by a unique clinical entity distinct from established clinical diagnoses.

The process of defining a new syndrome usually begins with a case definition that lists classification criteria to distinguish the potentially new patient population from patients with known clinical diagnoses. Development of the first case definition is a vital milestone intended to spur research and surveillance. More like a hypothesis than a conclusion, it is an early step in the process; it is often revised as more evidence comes to light. Case definitions usually are a mixture of clinical, demographic, and laboratory criteria. Clinical criteria are signs (physical-examination findings) and symptoms (subjective complaints of patients). Demographic criteria refer to age, sex, ethnicity, or other individual characteristics or exposure-related variables. Laboratory criteria refer to biologic measures of pathology or etiology (such as x-ray pictures and blood test results).

One method of developing an operational case definition is a statistical technique known as factor analysis (Ismail et al., 1999). Factor analysis is useful in identifying a small number of correlated variables from among a much larger number of observed variables, such as the symptoms that are reported in a survey of veterans. Factor analysis

[8]Registries rely on the ICD-9-CM (Joseph, 1997; Murphy et al., 1999).

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aggregates survey responses into statistical groupings of factors that might or might not have biologic plausibility or clinical relevance. Several researchers have used factor analysis in their studies (described later in this appendix) of the health of Gulf War veterans. When factor analysis is used in studies of veterans, the observed variables are measurements of veterans' symptoms, and the fundamental factors are symptom groupings that might represent a potential new syndrome. Any new syndrome (defined by factor analysis or other means) can have a distinct, albeit often unknown, etiology and pathogenesis (Taub et al., 1995). It is recognized that factor analysis has the potential to generate syndromes that might not be reproduced when a new population is examined.

When evidence is presented that the case definition—defined by factor analysis or other methods—successfully singles out a new patient population from comparison groups, the case definition may gain recognition by the medical establishment as a new syndrome (IOM, 2000). There are many advantages to defining and classifying a new syndrome, among them the creation of a more homogeneous patient population, which is a crucial step for determining prevalence and improving diagnosis and treatment. A potential disadvantage is the mislabeling or misclassification of a condition, which can thwart progress for years, if not decades (Aronowitz, 1991). Classification of a new patient population also stimulates further understanding of the natural history of a disease, risk factors, and ultimately etiology and pathogenesis. As more knowledge unfolds about etiology and pathogenesis an established syndrome can rise to the level of a disease. The renaming of a syndrome as a disease implies that the etiology or pathology has been identified.

Population-Based Studies

This section summarizes findings of population-based studies of Gulf War veterans. The next section summarizes findings of other types of epidemiologic studies. A population-based study is a methodologically robust type of epidemiologic study because its goal is to obtain information that is representative of the population of interest, in this case Gulf War veterans. The cohort may be the entire population of interest or a random selection from the population of interest. Population-based studies of Gulf War veterans sample a cohort of veterans by contacting them where they live, as opposed to where they seek treatment or where they serve in the military (such as a particular base or a particular branch of the service). Studies of military units or other military subgroups are less representative of the broader Gulf War veteran population than are population-based studies.

Large population-based studies of Gulf War veterans have been conducted in several countries that participated in the Gulf War coalition (the United States, Canada, Denmark, and the United Kingdom). They have shown consistent findings in the nature of unexplained symptoms and in their deleterious effects on functioning. Summary features of the studies appear in Table A.3 with those of other major epidemiologic studies.

Virtually all epidemiologic studies of Gulf War veterans, regardless of study design, rely on self-reports of symptoms and exposures. As discussed in Chapter 2, studies based on self-reports have inherent limitations because of potential inaccuracies in recall of past events and difficulty in verifying the reports. Most of the larger epidemiologic studies described here were conducted through mail or telephone surveys, which precluded clinical examination and diagnosis. Comparison groups were veterans of the same era who were not deployed to the Gulf War.

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TABLE A.3 Major Studies of Gulf War Veterans' Symptoms and Syndromes

Reference	Subjects/ Controls (*n*)	Study Design	Military Branch and Status	Response Rate (%)	Major Findings
Population-Based Studies					
Iowa Persian Gulf Study Group, 1997; Doebbeling et al., 2000	1896/1799	Population-based survey, factor analysis	All US branches and duty status	76	Symptoms (subjects vs controls) Fibromyalgia: 19.2% vs 9.6% Cognitive dysfunction: 18.7% vs 7.6% Depression: 17.0% vs 10.9% Three factors (somatic distress, psychological distress, and panic) higher in prevalence but not unique to Gulf War veterans
Kang et al., 2000, 2002	11,441/9476	Population-based survey, factor analysis	All US branches and duty status	70	All 48 symptoms significantly more common in deployed vs non-deployed ($p < 0.05$) Numerous chronic medical conditions reported twice as often (see Table A.5); possible neurological syndrome requiring further evidence
Goss Gilroy Inc., 1998	3113/3439	Survey	All Canadian Gulf War veterans	64.5	Symptoms Chronic fatigue (OR = 5.27) Cognitive dysfunction (OR = 4.36) Multiple chemical sensitivity (OR = 4.01)
Unwin et al., 1999; Ismail et al., 1999	2961/2620, 2614[a]	Population-based survey, factor analysis	UK Gulf War veterans (U. London)	65.1	Symptoms Fatigue (OR = 2.2) Posttraumatic stress (OR = 2.6) Psychological distress (OR = 1.6) Three factors (mood, respiratory system, peripheral nervous system) higher in prevalence, but not unique to Gulf War veterans
Cherry et al., 2001a; Cherry et al., 2001b	9585/4790[b]	Population-based survey, factor analysis	UK Gulf War veterans (U. Manchester)	85.5	Symptoms Almost all 95 symptoms were more common in deployed versus nondeployed. Numbness and tingling and widespread pain were about two times more prevalent Five factors (psychological, peripheral, respiratory, gastrointestinal, and concentration) higher in prevalence, but not unique to Gulf War veterans

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Reference	Subjects/ Controls (*n*)	Study Design	Military Branch and Status	Response Rate (%)	Major Findings
Ishoy et al., 1999b; Suadicani et al., 1999	821/400	Population-based survey, multivariate analysis	Danish peacekeeping veterans	58-84	Symptoms Greater prevalence of neuropsychological, gastrointestinal and dermatological symptoms, but not musculoskeletal, among deployed versus nondeployed About 21 percent of veterans reported a clustering of 3–5 neuropsychological symptoms vs 6.2 percent of controls ($p < 0.001$)
Other Epidemiologic Studies					
Haley et al., 1997b	249/no controls	Survey, factor analysis	Navy reserve	41	25% have one of six syndromes: impaired cognition, confusion–ataxia, arthro-myo-neuropathy, phobia–apraxia, fever–adenopathy, weakness–incontinence
Fukuda et al., 1998	1163/2538	Survey, clinical exam, factor analysis	Air Force National Guard and 3 other Air Force units	35–70	31 of 33 symptoms significantly more prevalent in Gulf War veterans; defined case as 1 or more symptoms from 2 of 3 categories: fatigue, mood-cognition, musculoskeletal; case not unique to Gulf War veterans
Proctor et al., 1998	300[c]/48	Survey or clinical interview	All US branches and duty status	38–62	PTSD diagnosis: 5, 7% vs 0% Dermatological symptoms (OR = 9.6, 6.9)[c] Gastrointestinal symptoms (OR = 8.0, 5.8)[c] Neuropsychological symptoms (OR = 6.4, 5.2)[c]

NOTE: OR = odds ratio; PTSD = posttraumatic stress disorder.
[a]Two comparison groups (Bosnia, Gulf era).
[b]The deployed group consisted of a main cohort ($n = 4795$) and a validation cohort ($n = 4790$).
[c]The 300 Gulf War veterans came from two study groups—one from Ft. Devens and the other from New Orleans. The control group was deployed to Germany.

The Iowa Study

The "Iowa study," a major population-based study of US Gulf War veterans, was a cross-sectional survey of a representative sample of 4886 military personnel who listed Iowa as their home of record at the time of enlistment (Iowa Persian Gulf Study Group, 1997). The study examined the health of military personnel in all branches of service who were still serving or had left service. The sample was randomly selected from and representative of about 29,000 military personnel. Of the eligible study subjects, 3695 (76%) completed a telephone interview. Study subjects were divided into four groups, two that had been deployed to the Gulf War and two that had not been. Trained examiners using standardized questions,

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instruments, and scales interviewed the subjects.[9] The two groups of Gulf War military personnel reported roughly twice the prevalence of symptoms suggestive of the following conditions: fibromyalgia, cognitive dysfunction, depression, alcohol abuse, asthma, posttraumatic stress disorder (PTSD), sexual discomfort, and chronic fatigue (Table A.4).[10] Furthermore, on a standardized instrument for assessing functioning (the Medical Outcome Study's 36-item questionnaire known as the Short Form-36, or SF-36), Gulf War veterans displayed significantly lower scores in all eight subscales for physical and mental health. The subscales profile aspects of quality of life. The subscales for bodily pain, general health, and vitality showed the greatest absolute differences between deployed and nondeployed veterans. In short, this large, well-controlled study demonstrated that some sets of symptoms were more frequent and quality of life poorer among Gulf War veterans than among nondeployed military controls.

Symptom clustering. The Iowa study was the first major population-based study to group sets of symptoms into categories suggestive of existing syndromes or disorders, such as fibromyalgia or depression. Its finding of considerably higher prevalence among Gulf War veterans of symptom groups suggestive of fibromyalgia, depression, and cognitive dysfunction (see Table A.4) motivated other researchers to examine—through factor analysis—the potential for a new syndrome that would group and classify veterans' symptoms. Several years later, the same team of investigators performed a factor analysis on the Iowa cohort (Doebelling et al., 2000). They identified three symptom factors in deployed veterans—somatic distress, psychologic distress, and panic—but the factors were not exclusive to deployed veterans. Thus, the study did not support the existence of a new syndrome.

Exposure–symptom relationships. The Iowa study assessed exposure–symptom relationships by asking veterans to report on their exposures in the Gulf War. Researchers found that many of the self-reported exposures were significantly associated with health conditions. For example, symptoms of cognitive dysfunction were found to have been associated with self-reports of exposure to solvents or petrochemicals, smoke or combustion products, lead from fuels, pesticides, ionizing or nonionizing radiation, chemical-warfare agents, use of pyridostigmine, infectious agents, and physical trauma. A similar set of exposures was associated with symptoms of depression or fibromyalgia. The study concluded that no exposure to any single agent was related to the conditions that the authors found to be more prevalent in Gulf War veterans (Iowa Persian Gulf Study Group, 1997).

[9]Sources of questions included the National Health Interview Survey, the Behavioral Risk Factor Surveillance Survey, the National Medical Expenditures Survey, the Primary Care Evaluation of Mental Disorders, the Brief Symptom Inventory, the CAGE questionnaire, the PTSD (Posttraumatic Stress Disorder) Checklist—Military, the Centers for Disease Control and Prevention Chronic Fatigue Syndrome Questionnaire, the Chalder Fatigue Scale, the American Thoracic Society questionnaire, and the Sickness Impact Profile.

[10]The conditions listed were not diagnosed, because no clinical examinations were performed. Rather, before conducting their telephone survey, researchers grouped sets of symptoms from their symptom checklists into *a priori* categories of diseases or disorders. After a veteran identified himself or herself as having the requisite set of symptoms, researchers analyzing responses considered the veteran as having symptoms "suggestive" of or consistent with a particular disorder but not as having a formal diagnosis of the disorder.

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TABLE A.4 Results of the Iowa Study

Symptoms (in order of frequency)[a]	Prevalence in Gulf War Veterans (%)	Prevalence in Non-Gulf War Veterans (%)
Fibromyalgia	19.2	9.6
Cognitive dysfunction	18.7	7.6
Alcohol abuse	17.4	12.6
Depression	17.0	10.9
Asthma	7.2	4.1
PTSD	1.9	0.8
Sexual discomfort	1.5	1.1
Chronic fatigue	1.3	0.3

SOURCE: Iowa Persian Gulf Study Group, 1997.
[a]Based on survey instrument designed by investigators to incorporate structured instruments and standardized questions.

VA Study

A major population-based study of US veterans was mandated by Public Law 103-446. It is a retrospective cohort study conducted by VA. Its purpose is to estimate the prevalence of symptoms and other health outcomes in Gulf War veterans versus non–Gulf War veterans.[11] This population-based survey had three phases. The first phase was a questionnaire mailed to 30,000 veterans. The second phase validated self-reported data with medical-record review and analyzes characteristics of those who did not respond to the mailed survey. The third phase is a comprehensive medical examination and laboratory testing of a random sample of 2000 veterans drawn from both the Gulf War and the comparison group (Research Working Group, 1998). The purpose of the third phase is to establish diagnoses that will make it possible to see what proportion of self-reported symptoms are due to established diseases rather than unexplained illnesses. The findings of only the first two phases have been published.

The study was designed to be representative of the nearly 700,000 US veterans sent to the Persian Gulf and 800,680 non-Gulf veterans of the same era. Questionnaires were mailed to a stratified random sample of 15,000 Gulf War and 15,000 non-Gulf War veterans identified by DOD and representing various military branches and units. The questionnaires contained a list of 48 symptoms and questions about chronic medical conditions, functional limitations, and other items from the National Health Interview Survey. A questionnaire about exposures was also included. The response rate was about 70%.

The investigation found significantly higher symptom prevalence of all 48 symptoms among Gulf War veterans (Kang et al., 2000). Four of the 10 most frequently reported symptoms are runny nose, headache, unrefreshing sleep, and anxiety (Table A.5). Numerous chronic medical conditions—such as sinusitis, gastritis and dermatitis—were reported more frequently among Gulf War veterans; many were reported twice as often. Ten symptoms and 12 medical conditions were remarkably similar in prevalence to those in a UK cohort (Unwin et al., 1999). Finally, Gulf War veterans reported significantly higher rates of functional impairment (27.8% versus 14.2%), limitations of employment (17.2% versus 11.6%), and health-care use, as assessed by clinic visits (50.8% versus 40.5%) or hospitalizations (7.8% versus 6.4%). In a randomly selected subset of veterans, medical-record reviews verified more than 90% of self-reported reasons for clinic visits or hospitalizations.

[11]Health outcomes include reproductive outcomes in spouses and birth defects in children.

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Symptom clustering. The VA study searched for potentially new syndromes through factor analysis. A separate article by Kang and colleagues (2002) found that 47 symptoms reported by veterans yielded six factors, only one of which contained a cluster of neurologic symptoms that did not load on any factors in the non-Gulf War deployed veterans. The symptoms in the cluster were 1) loss of balance/dizziness; 2) speech difficulty; 3) blurred vision; and 4) tremors/shaking. A group of 277 deployed veterans (2.4 percent) versus 43 non-deployed veterans (0.45 percent) met a case definition subsuming *all* four symptoms. The authors interpreted their findings as suggesting a possible unique syndrome related to Gulf War deployment that requires objective supporting clinical evidence.

TABLE A.5 Results of the VA Study

10 Most Common Self-Reported Symptoms[a]	Prevalence in Gulf War Veterans (%)	Prevalence in Non-Gulf War Veterans (%)
Runny nose	56	43
Headache	54	37
Unrefreshing sleep	47	24
Anxiety	45	28
Joint pain	45	27
Back pain	44	30
Fatigue	38	15
Ringing in ears	37	23
Heartburn	37	25
Difficulty sleeping	37	21

5 Most Common Self-Reported Chronic Medical Conditions[a]	Prevalence in Gulf War Veterans (%)	Prevalence in Non-Gulf War Veterans (%)
Sinusitis	38.6	28.1
Gastritis	25.2	11.7
Dermatitis	25.1	12.0
Arthritis	22.5	16.7
Frequent diarrhea	21.2	5.9

SOURCE: Kang et al., 2000.

[a]For symptoms, subjects were asked whether symptoms were recurring or persistent during the previous 12 months. The differences in prevalence all are statistically significant ($p < 0.05$).

Exposure–symptom relationships. A nested case–control analysis was performed on those who met the case definition to determine which of 23 self-reported exposures were more common among cases versus controls (Kang et al., 2002). Of nine exposures that were at least three times higher among deployed cases, two were solvent-related: CARC paint (51.2 percent in cases vs 16.3 percent in controls) and chemically contaminated food (73.4 percent in cases vs 20.6 percent in controls). No pesticide-related exposures were reported three or more times more frequently in cases versus controls. Dose-response was not studied because of the nature of the dataset regarding self-reported exposure.

The article covering the large cohort (Kang et al., 2000) did not assess exposure-symptom relationships. It reported on exposures only by compiling the percentages of veterans who reported each of 23 environmental exposures and nine vaccine or prophylactic exposures (such as to pyridostigmine bromide). The five most common environmental exposures reported by more than 60% of survey participants were to diesel, kerosene, or other petrochemical fumes; to local food other than that provided by the armed forces; to chemical protective gear; to smoke from oil-well fires; and to burning trash or feces. Table

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A.6 lists the percentages of veterans reporting pesticide or solvent-related exposures of interest to the committee.

TABLE A.6 VA Study Percent Distribution of Self-Reported Exposures (n = 11,441)

Self-Reported Exposures	Percentage
Personal pesticides, including creams, sprays and flea collars	48.4
Contact with prisoners of war[a]	32.8
Food contaminated with smoke, oil, or other chemicals	30.2
Other paint or solvent or petrochemicals substances	29.7
Chemical Agent Resistant Compound Paint	21.7

SOURCE: Kang et al., 2000
[a]Lindane used as delousing agent (Cecchine et al., 2000)

Oregon and Washington Veterans

Veterans from Oregon or Washington were studied in a series of analyses by investigators of the Portland Environmental Hazards Research Center (McCauley et al., 1999). A questionnaire was sent to a random sample (n = 2343) of 23,711 Gulf War veterans listing Oregon or Washington as their home state of record at the time of deployment. The response rate was 56%. The study found high rates (20–60%) of self-reported symptoms, including cognitive-psychologic symptoms, unexplained fatigue, musculoskeletal pain, gastrointestinal complaints, and rashes. However, among the first 225 participants who later came for a clinical examination, there were significant differences between their self-reported symptoms on questionnaires and their symptoms reported at clinical examination. Significantly fewer veterans reported symptoms at clinical examination.

Symptom clustering. Investigators studied clusters of unexplained symptoms by creating a new case definition for unexplained illness (Storzbach et al., 2000). Cases were identified through questionnaires as meeting a threshold number, combination, and duration of fatigue, cognitive/psychologic, and musculoskeletal symptoms. Veterans whose symptom clusters remained unexplained at clinical examination (after exclusion of established diagnoses) were defined as constituting cases. Controls were those who at the time of clinical examination had no history of case-defining symptoms during or after their service in the Gulf War. In an analysis of the 241 cases versus 113 controls, investigators found small but statistically significant deficits in cases on some neurobehavioral tests of memory, attention, and response speed. Cases also were significantly more likely to report increased distress and psychiatric symptoms (Storzbach et al., 2000). A later analysis focused on a subgroup of 30 (of the 241) cases whose performance was slowest on the Oregon Dual Task Procedure (ODTP), a relatively new test of digit recognition that assesses motivation, attention, and memory (Storzbach et al., 2001). In comparison with other cases, the "slow ODTP" group performed more poorly on other neurobehavioral tests of memory, attention, and reaction time but not on psychologic tests. Investigators plan more-extensive imaging and EEG tests on this subgroup of cases.

Exposure–symptom relationships. Another nested case–control analysis of the population-based cohort examined whether cases of unexplained illness were more common in any of the three periods of Gulf War deployment: precombat, combat, and postcombat (Spencer et al., 1998). Subjects were not asked about specific exposures, but their period of deployment was used as a proxy for different combinations of environmental exposures. Of 14 potential exposures likely to be differentially encountered during deployment periods, two were of special interest to the committee: "insect repellent" and "pesticides." Those two

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exposures were more common in the precombat and postcombat periods than in the combat period. The sample consisted of 244 veterans with unexplained illness and 113 healthy controls. The vast majority of subjects with unexplained illness served in more than one of the three deployment periods. In the few cases with service in only one of the periods, there were no statistically significant differences in prevalence between periods, although there was a trend for cases to be more common in veterans who served in the postcombat period. Those findings suggest that cases do not readily fall into distinct deployment periods.

The Canadian Study

The findings of a 1997 survey (Goss Gilroy Inc., 1998) mailed to the entire cohort of Canadian Gulf War veterans were similar to those of the Iowa study. Respondents from Canada who had been deployed to the Gulf War (n = 3113) were compared with respondents deployed elsewhere (n = 3439) during the same period. Of the Gulf War veterans responding, 2924 were male and 189 were female. Deployed forces had significantly higher rates of self-reported chronic conditions and symptoms of a variety of clinical outcomes[12]—(chronic fatigue, cognitive dysfunction, multiple chemical sensitivities, major depression, PTSD, chronic dysphoria, anxiety, fibromyalgia, and respiratory diseases)—than controls. The greatest differences between deployed and nondeployed forces were in the first three outcomes. The symptom grouping with the highest overall prevalence was cognitive dysfunction, which occurred in 34–40% of Gulf War veterans compared with 10–15% of control veterans. Gulf War veterans also reported significantly more visits to health-care practitioners, greater dissatisfaction with their health status, and greater health-related reductions in recent activity than control veterans.

Symptom clustering. The Canadian study did not search for potentially new syndromes.

Exposure–symptom relationships. In Canadian Gulf War veterans, the greatest number of symptom groupings was associated with self-reported exposures to psychologic stressors and physical trauma. Several symptom groupings also were associated with exposure to chemical-warfare agents, nonroutine immunizations, sources of infectious diseases, and ionizing or nonionizing radiation. Nevertheless, a subset of Canadian veterans who could not have been exposed to many of the agents, because they were based at sea, reported symptoms as frequently as did land-based veterans.

The UK Studies

The UK sent 53,000 personnel to the Gulf War. The UK's centralized health delivery systems enabled researchers to readily retrieve service records. From the pool of veterans, two teams of researchers each studied a separate, nonoverlapping, stratified random sample of Gulf War veterans. One team was from the University of London (Guy's, King's, and St. Thomas's Medical School), and the other team was from the University of Manchester.

Unwin and collaborators (1999) at the University of London investigated the health of servicemen from the UK in a population-based study. The study used a random sample of the entire UK contingent deployed to the Gulf War[13] and two comparison groups. One of the

[12]Several of the reported health conditions or symptoms were combined to define clinically meaningful outcomes (Goss Gilroy Inc., 1998).

[13]UK military personnel in the Gulf War were somewhat different from US personnel in demographics, combat experience, and exposures to particular agents (U.K. Ministry of Defence, 2000).

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comparison groups was deployed to the conflict in Bosnia (n = 4250); this made the study the only one to use a comparison population with combat experience during the time of the Gulf War. The second comparison group (n = 4246) was deployed to other noncombat locations outside the UK in the same timeframe. Through a mailed questionnaire, the investigators asked about symptoms (50 items), medical disorders (39 items), functional capacity, and other topics. The findings for the Gulf War cohort and comparison cohorts were compared through calculation of odds ratios (ORs). The study controlled for potential confounding factors (including sociodemographic and lifestyle factors) by logistic regression analysis. Only male veterans' results were analyzed, because female veterans' roles and symptoms were distinct enough to warrant separate consideration.

The UK Gulf War-deployed veterans (n = 4248) reported higher prevalence of symptoms and diminished functioning than did either comparison group. Gulf War veterans were 2–3 times more likely than comparison subjects to have met symptom-based criteria for chronic fatigue, posttraumatic stress reaction, and "chronic multisymptom illness," the label for the first case definition[14] developed by Centers for Disease Control and Prevention (CDC) researchers to probe for the existence of a potential new syndrome among Gulf War veterans (Fukuda et al., 1998). That the Bosnia cohort in the UK study, which was deployed to a combat setting, reported fewer symptoms than the Gulf War cohort suggests that combat deployment itself does not account for higher symptom reporting.

A separate analysis of this UK Gulf War cohort found that the prevalence of multiple chemical sensitivity (MCS)[15] was 1.3%, a rate significantly greater than in the comparison groups. The prevalence of chronic fatigue syndrome at 2.1% was not significantly greater (Reid et al., 2001).

Symptom clustering. In a companion study using the UK data set, Ismail and colleagues (1999) set out to determine whether the symptoms that occurred with heightened prevalence in UK Gulf War veterans constituted a new syndrome. By applying factor analysis, they were able to identify three fundamental factors, which they classified as related to mood, respiratory system, and peripheral nervous system. The pattern of symptom reporting by Gulf War veterans differed little from the patterns by Bosnia and Gulf War-era comparison groups, although the Gulf War cohort had a higher frequency of symptom reporting. Furthermore, the study did not identify in this cohort the six factors characterized by Haley and colleagues (1997b) in their factor-analysis study described in the next section. The UK authors interpreted their results as evidence against the existence of a unique Gulf War syndrome. Nevertheless, in a later study of veterans' beliefs, the authors found that 17.3% of UK Gulf War veterans believed that they had a condition known as Gulf War syndrome (Chalder et al., 2001).

Exposure–symptom relationships. In the UK Gulf War cohort, most self-reported exposures were associated with all of the health outcomes; that was also true for the two comparison cohorts (Unwin et al., 1999). The authors interpreted that finding as evidence that the exposures were not uniquely associated with Gulf War illnesses. Veterans with symptoms, regardless of deployment status, were more likely to report a wide variety of exposures than those without symptoms. Within the Gulf War cohort, two vaccine-related

[14]A case is defined as having one or more chronic symptoms in at least two of these three categories: fatigue, mood–cognition (for example, feeling depressed or difficulty in remembering or concentrating), and musculoskeletal (joint pain, joint stiffness, or muscle pain). This case definition was developed as a research tool to organize veterans' unexplained symptoms into a potentially new syndrome.

[15] Based on criteria of Simon and colleagues (1993).

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exposures—vaccination against biologic-warfare agents and receiving multiple vaccinations—were associated with the case definition of the chronic multisymptom illness developed by CDC researchers (Fukuda et al., 1998). A later analysis of the data on a subcohort of UK veterans found that receiving multiple vaccinations during deployment was associated with five of the six health outcomes examined, including multisymptom illness as defined by CDC (Hotopf et al., 2000). Analysis of the subgroup of veterans meeting case criteria for MCS found that they were significantly more likely to report several types of pesticide exposures (Reid et al., 2001). Veterans meeting case criteria for chronic fatigue syndrome were *not* more likely to report pesticide exposure but were more likely to report combat-related injury (Reid et al., 2001).

The University of Manchester study used a random sample of UK veterans' years after the Gulf War (Cherry et al., 2001a). The cohort was separate from that studied by Unwin and colleagues (1999). Two groups of veterans deployed to the Gulf War (n = 9585, a main cohort and a validation cohort) were compared with veterans who were not deployed but whose health would not have prevented deployment (n = 4790). Veterans were sent a questionnaire about the extent to which they were burdened by 95 symptoms in the previous month. By asking them to mark their answers on a visual analogue scale, investigators sought to determine the degree of symptom severity. Investigators also sought to determine areas of peripheral neuropathy by asking veterans to shade body areas on two mannequins in which they were experiencing pain or numbness and tingling. On almost all 95 symptoms, deployed veterans reported higher symptom severity. The overall mean symptom severity score was similar in the two Gulf War cohorts and significantly greater than that for the non-Gulf War cohort. For 14 symptoms—including memory, concentration, and mood problems—the severity scores of deployed veterans were at least twice those of the nondeployed. Numbness and tingling were reported by about 14% of deployed and about 7% of nondeployed. Widespread pain was also reported more frequently (12.2% versus 6.5%).

Symptom clustering. Through factor analysis, the investigators identified seven factors, which accounted for 48% of the variance. Deployed veterans' scores were significantly different on five of them: psychologic, peripheral, respiratory, gastrointestinal, and concentration factors. No difference was found in the neurologic factor, and appetite, the final factor, was significantly lower than in the non-Gulf War cohort. None of the factors was exclusive to Gulf War veterans, so the investigators concluded that their findings did not support a new syndrome (Cherry et al., 2001a).

Exposure–symptom relationships. The two UK Gulf War cohorts completed a second questionnaire with details of the dates when they were sent to each location and the exposures they had experienced. The exposure questionnaire contained 14 exposures. The main analysis involved a multiple regression of each of the seven factors on all exposures and other potential confounders. Many of the reported exposures correlated with one another. In the multivariate regression analysis, the number of days that veterans handled pesticides was related to the overall severity score and to the peripheral and neurologic factors. The number of days when they applied insecticide to their skin was related to severity and to the peripheral, respiratory, and appetite factors. The number of inoculations was associated with skin and musculoskeletal symptoms. There was a marked dose-response gradient for the association between insect repellents and the peripheral and respiratory

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factors. A dose-response gradient for the association of handling pesticides with the peripheral factor was present but less robust. The handling of pesticides was associated with peripheral neuropathy (OR = 1.26, $p < 0.001$), and the use of insect repellent was associated with widespread pain (OR = 1.15, $p < 0.001$). Respraying vehicles and living in sprayed quarters were not associated with any health outcomes. Because the ORs were only slightly increased, the investigators interpreted weak relationships between symptoms and exposures (Cherry et al., 2001b).

The Danish Study

Troops from Denmark were primarily involved in peace-keeping or humanitarian roles after the end of the Gulf War. They were studied in a series of population-based studies (Ishoy et al., 1999b; Suadicani et al., 1999). A total of 821 veterans were eligible by virtue of having served any time in the period August 1990 to December 1997. Because Danish troops in the Gulf War were successively replaced every 6 months, most respondents were not there until years after the end of the war. About 60% were deployed from 1992 to 1994, and 20% after 1995. The Gulf War veterans were matched by age, sex, and profession to 400 members of the Danish armed forces who were not deployed to the Gulf War. Symptom and exposure questionnaires and health examinations were used. Findings of health examinations were not used in the study's analysis of symptom-exposure relationships.

Of 22 neuropsychologic symptoms, 17 were significantly more prevalent among Gulf War veterans than among controls. Many of the symptoms were correlated with one another. Headache and fatigue-related symptoms were present in about 20% of deployed versus up to 10% of nondeployed. Gastrointestinal symptoms and diseases and symptoms related to the skin or allergy were more frequent in deployed veterans. The pattern of symptoms, except musculoskeletal symptoms (which were not more prevalent), was similar to the patterns seen in the UK, VA, and Canadian cohorts. The investigators concluded that the overlap of symptoms between veterans deployed during and after the war indicated the existence of common risk factors independent of exposure to war itself.

Symptom clustering. The authors did not use factor analysis, but they did use a multiple logistic regression analysis with adjustments for age and sex to find the most relevant neuropsychologic symptoms (Suadicani et al., 1999). Only five of the 17 symptoms remained significant after adjustment for the interrelationship of variables. About 21% of veterans reported a clustering of three to five of the relevant symptoms versus 6.2% of controls ($p < 0.001$). Relevant symptoms included concentration or memory problems, repeated fits of headache, balance disturbances or fits of dizziness, abnormal fatigue not caused by physical activity, and problems in sleeping all night. The symptoms excluded from further analysis included numbness or tingling in hands and feet, suddenly diminished muscular power, and tingling or shivering of arms, legs, or other parts of the body.

Exposure–symptom relationships. One of the analyses investigated whether 22 neuropsychologic symptoms were associated with 18 self-reported environmental exposures[16] (Suadicani et al., 1999). Most exposures were significantly associated with three to five relevant neuropsychologic symptoms in a univariate analysis. Four exposures, especially "bathing in or drinking contaminated water (fumes, oil, chemicals)," remained significant after adjustment in a multiple logistic model that adjusted for associations of

[16]Exposures did not include pyridostigmine bromide or vaccinations against chemical- or biologic warfare agents, because Danish veterans had a peace-keeping role and thus were not at risk for chemical or biologic warfare.

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exposures with one another. The exposure–symptom findings are discussed further in the body of this report. A separate multivariate analysis of gastrointestinal symptoms found them to be associated with two exposures: burning of waste or manure and exposure to insecticide against cockroaches (Ishoy et al., 1999a).

Other Studies of Veterans' Symptoms and General Health Status

One of the first epidemiologic studies of US Gulf War veterans was of more than 4000 active-duty and reserve personnel from Pennsylvania and Hawaii (Stretch et al., 1995). Veterans deployed to the Gulf War reported higher prevalence of 21 of 23 symptoms on a symptom checklist than nondeployed veterans (although the total response rate was only 31%). Overall, deployed veterans were about 2–4 times more likely than nondeployed veterans to report each symptom.

The symptom experience of two cohorts of Gulf War veterans from Massachusetts (Ft. Devens) and New Orleans was studied by Proctor and colleagues (1998). In comparison with veterans deployed to Germany during the Gulf War era, stratified random samples of both Gulf War cohorts had increased prevalence of 51 of 52 items on a health-symptom checklist. The greatest differences in prevalence of reported symptoms were for dermatologic symptoms (such as rash, eczema, and skin allergies), neuropsychologic symptoms (such as difficulty in concentrating and difficulty in learning new material), and gastrointestinal symptoms (such as stomach cramps and excessive gas). The study's nearly 300 subjects represented a stratified random sample of 2949 troops from Ft. Devens and 928 troops from New Orleans; both groups consisted of active-duty, reserve, and National Guard troops. The cohorts were also the focus of several studies of stress-related disorders (discussed later in this appendix).

Female Air Force veterans were studied by Pierce (1997), who examined a stratified sample of 525 women (active-duty, National Guard, and reserve) drawn from all 88,415 women who served in the Air Force during the Gulf War era. Women deployed to the Gulf War reported rash, cough, depression, unintentional weight loss, insomnia, and memory problems more frequently than women deployed elsewhere. The pattern of symptom reporting was similar to that reported by men and women who participated in the Iowa study. In addition, women deployed to the Gulf War were more likely than controls to report sex-specific problems, such as breast cysts and lumps and abnormal cervical cytology.

The first published study to search for new syndromes was conducted by Haley and collaborators (1997b), who studied a battalion of naval reservists called to active duty for the Gulf War (n = 249). More than half the battalion had left the military by the time of the study. Of those participating, 70% reported having had a serious health problem since returning from the Gulf War, and about 30% reported having no serious health problems. The study was the first to cluster symptoms into new syndromes by applying factor analysis. Through standardized symptom questionnaires and two-stage factor analysis, the investigators defined what they considered to be either six syndromes or six variants of a single syndrome, which they labeled impaired cognition, confusion–ataxia, arthromyoneuropathy, phobia–apraxia, fever–adenopathy, and weakness–incontinence. One-fourth of the veterans in this uncontrolled study (n = 63) were classified as having one of the six syndromes. The first three syndromes had the strongest factor clustering of symptoms.

In a followup study of the same cohort, Haley and colleagues (1997a) used a case–control design to examine neurologic function. They chose as cases the 23 veterans who had

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scored highest on the three syndromes with the strongest factor clustering. The results of extensive neurologic and neurobehavioral testing demonstrated that cases had significantly greater evidence of neurologic dysfunction when compared with two small groups of healthy controls from the same battalion.[17] Investigators concluded that the three syndromes, derived from factor analysis of symptoms, may signify variant forms of expression of a generalized injury to the nervous system.[18] In a later study, cases with one of the three syndromes were more likely than healthy controls to exhibit vestibular dysfunction (Roland et al., 2000). Related research on the same subset of veterans has found evidence of basal ganglia and brainstem neuronal loss via magnetic resonance spectroscopy (Haley et al., 2000).

The three syndromes identified by Haley and colleagues (1997b) were the focus of a companion case–control study that examined their relationship to self-reported exposures to neurotoxicants. The study tested the hypothesis that exposure to organophosphates and related chemicals that inhibit cholinesterase is responsible for the three nervous system-based syndromes (Haley and Kurt, 1997). Each of the syndromes was associated with a distinct set of risk factors. The impaired-cognition syndrome was found, through multiple logistic regression, to be associated with jobs in security and the wearing of flea-and-tick collars. The confusion–ataxia syndrome was associated with self-reports of having been involved in a chemical-weapons attack and of having advanced adverse effects of pyridostigmine bromide.[19] Finally, arthromyoneuropathy was associated with higher scores on the scale of advanced adverse effects of pyridostigmine bromide and with an index created by the investigators to enable veterans to self-report the amount and frequency of their use of government-issued insect repellent. The authors concluded that some Gulf War veterans had delayed, chronic nervous system syndromes as a result of exposure to combinations of neurotoxic chemicals (Haley and Kurt, 1997).

Another study by Haley and collaborators (1999) examined whether genetic susceptibility could play a role in placing some veterans at risk for neurologic damage by organophosphate chemicals. They hypothesized that neurologic symptoms in ill veterans might be explained by their having genetic polymorphisms (variations) in metabolizing enzymes. One set of polymorphisms could impair their ability to detoxify organophosphates (such as sarin, soman, and some pesticides) rapidly. The investigators studied 45 veterans, 25 with chronic neurologic symptoms as identified through their earlier factor-analysis study and 20 healthy controls from the same battalion. They measured blood butyrylcholinesterase and two types, or allozymes, of paraoxonase/arylesterase 1. The genotypes encoding the allozymes were also studied. The investigators found that veterans who were ill had blood butyrylcholinesterase levels similar to those of control subjects; however, ill veterans had lower type Q paraoxonase/arylesterase, the allozyme that hydrolyzes sarin rapidly. They also were more likely to have the type R genotype, which encodes the allozyme that has low hydrolyzing activity for sarin. The authors interpreted their findings as suggesting that

[17]One group of healthy controls (n = 10) was deployed to the Gulf War; the other (n = 10) was not.

[18]Neuropsychologic or neurologic impairments have been the focus of several smaller studies as well. Some found subtle changes in nerve-conduction velocity and cold sensation (Jamal et al., 1996) and in some tests of finger dexterity and executive functioning (Axelrod and Milner, 1997); others found no significant differences in measures of nerve conduction and neuromuscular functioning (Amato et al., 1997) or neuropsychologic performance (Goldstein et al., 1996).

[19]The scale for adverse effects of pyridostigmine bromide was developed by the investigators to measure less-common adverse effects, such as excessive sweating, tearing, chest tightness, nausea, muscle twitching, muscle cramps, headache, and pounding heartbeat.

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reduced ability to detoxify environmental chemicals may have contributed to the onset of neurological symptoms in some Gulf War veterans.

A large study by Fukuda and colleagues (1998) used factor analysis and other methods to assess the health status of Gulf War veterans. By studying an Air Force National Guard unit from Pennsylvania and three comparison Air Force populations, the investigators aimed to organize symptoms into a case definition and to carry out clinical evaluations on a subset of veterans. Of 3701 veterans surveyed, those deployed to the Gulf War experienced higher prevalence of chronic symptoms (33 of 35 symptoms with more than 6-month duration were reported to be more prevalent) than nondeployed veterans. The authors then used two methods to derive a case definition: factor analysis and a clinical approach. The two approaches yielded similar case definitions, and the investigators chose the latter for its simplicity of application in research.

The authors defined a case of chronic multisymptom illness as having one or more chronic symptoms from at least two of three categories: fatigue, mood–cognition symptoms (for example, feeling depressed and difficulty in remembering or concentrating), and musculoskeletal symptoms (joint pain, joint stiffness, or muscle pain). According to that definition, 39% of Gulf War-deployed veterans and 14% of nondeployed veterans had mild to moderate cases, whereas 6% and 0.7%, respectively, had severe cases. On the basis of a total of 158 clinical examinations in one unit, there were no abnormal physical or laboratory findings among those who met the case definition. Cases reported significantly lower functioning and well-being.

A sizable fraction (14%) of nondeployed veterans also met the mild-to-moderate case definition. The investigators concluded that their case definition could not specifically characterize Gulf War veterans with unexplained illnesses (Fukuda et al., 1998). The study, however, had several limitations, the most important of which was its coverage of only active Air Force personnel (several years after the Gulf War), which limits its generalizability to other branches of service and to those who left the service possibly because of illness.

To assess risk factors, the authors performed clinical evaluations on a subset of veterans (n = 158), all of whom volunteered for the evaluation and came from the index unit of the Pennsylvania Air Force National Guard. Of the members of this unit, 45% had been deployed to the Gulf War. Overall, there was a dearth of abnormal findings from blood, stool, and urine testing among those who met the case definition for chronic multisymptom illness. There were no differences between cases and noncases in the proportion that seroreacted to botulinum toxin, anthrax protective antigen, leishmanial antigens, and other antigens. This was among the few studies to have assessed exposures (mostly to infectious diseases) via laboratory testing, as opposed to self-reports, but the sample undergoing clinical evaluation was relatively small and restricted to Air Force National Guard members.

A nested case–control study of the same cohort (n = 1002) sought to identify self-reported exposures associated with cases of chronic multisymptom illness (Nisenbaum et al., 2000). It found that meeting the case definition of severe and mild-to-moderate illness was associated with use of pyridostigmine bromide, use of insect repellent, and belief in a threat from biologic or chemical weapons. Having an injury requiring medical attention was also associated with having a severe case of chronic multisymptom illness.

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EPIDEMIOLOGIC STUDIES OF SPECIFIC HEALTH END POINTS

Mortality Studies

A large mortality study of nearly all Gulf War-deployed veterans identified no excess postwar mortality, with the exception of a rise in death from motor-vehicle accidents (Kang and Bullman, 1996). The study examined mortality patterns through 1993 by using two databases, 1) the VA Beneficiary Identification and Records Locator Subsystem and 2) deaths reported to the Social Security Administration.[20] It compared deployed veterans with a similarly sized cohort of veterans who did not serve in the Gulf War. The most recent publication by the authors found that by 1997 the excess mortality risk from motor-vehicle accidents had disappeared, a finding consistent with the mortality pattern after the Vietnam War (Kang and Bullman, 2001).

A second mortality study of US active-duty military personnel focused exclusively on the Gulf War period. It compared noncombat mortality among troops stationed in the Gulf War and troops on active duty elsewhere. There was no excess noncombat mortality in deployed veterans, except for unintentional injury (due to vehicle accidents and other causes; Writer et al., 1996). Similarly, a recently published study of UK veterans of the Gulf War in relation to contemporaneous controls found no increase in mortality other than an increase in accidental death (Macfarlane et al., 2001).

The principal limitation of published mortality studies is the short duration of their followup observation. More time must elapse before excess mortality would be expected from illnesses with long latency, such as cancer, or with a gradually deteriorating course, such as multiple sclerosis.[21]

Hospitalization Studies

The risk of hospitalization was the subject of two large studies of active-duty personnel discharged from DOD hospitals before and after the Gulf War. The first study compared almost 550,000 Gulf War veterans with almost 620,000 nondeployed veterans and found no significant and consistent differences in hospitalizations after the war (Gray et al., 1996). Before the Gulf War, from 1988 to 1990, those later deployed to the Persian Gulf were at lower risk for hospitalization than their nondeployed counterparts, probably because of the healthy-warrior effect. To permit valid before-after comparisons, the investigators used statistical methods to remove bias introduced by the "healthy-warrior effect" (also called the "healthy-worker effect").

A second hospitalization study re-examined the same dataset of active-duty personnel discharged from DOD hospitals to search for excess hospital admissions for

[20]The degree of completeness of using these record systems was assessed with a validation study that used state vital-statistics data. Ascertainment was estimated at 89% of all deaths in the Gulf War cohort and comparison group.

[21]Critics assert that the mortality study by Kang and Bullman (1996) made errors in calculating confidence intervals around mortality and did not adequately account for the "healthy-warrior effect," the possibility that troops mobilized to the Gulf War were healthier than nondeployed troops and thereby biased the study toward not finding a mortality difference (Haley, 1998). The study authors disagreed and demonstrated that other statistical techniques, recommended by critics, had negligible impact on their confidence intervals (Kang and Bullman, 1998). To counter the charge of selection bias, the study authors pointed out that effects of any potential selection bias were minimal inasmuch as they found no differences in mortality risk between troops mobilized to sites other than the Gulf War and troops not mobilized at all (Kang and Bullman, 1998).

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unexplained illnesses. The authors reasoned that the first study might have missed hospitalizations for a new or poorly recognized syndrome. Hospital discharge coding might have inconsistently classified such hospitalizations by many diagnoses and masked an effect if one were present. The second study operationally defined unexplained illnesses as diagnoses falling into several catchall *International Classification of Diseases, Ninth Revision—Clinical Modification* (ICD-9-CM) diagnostic categories comprising nonspecific infections and other ill-defined conditions. After adjusting for hospitalizations only for evaluation (as opposed to treatment) in the DOD registry program, the authors found no significant differences between deployed and nondeployed active-duty military (Knoke and Gray, 1998).

Those hospitalization studies provide some reassurance that excess hospitalizations did not occur among veterans of the Gulf War who remained on active duty through 1993. Like the mortality studies, however, they did not capture illnesses that might have longer latency, such as cancer, or illnesses in people separated from the military and admitted to nonmilitary (VA and civilian) hospitals (Haley, 1998). The studies did not measure the use of outpatient treatment and thus only detected illnesses that required hospitalization (Gray et al., 1996; Knoke and Gray, 1998).

Studies of Birth Defects and Reproductive Outcomes

Several studies failed to identify an excess of birth defects in offspring of deployed versus nondeployed veterans. A small study of two Mississippi National Guard units (n = 282) deployed to the Gulf War found no excess rate of birth defects in National Guard members' children compared with rates expected on the basis of surveillance systems and previous surveys (Penman et al., 1996). A much larger study of all live births in military hospitals (n = 75,000), from 1991 to 1993, included a comparison population of births to nondeployed personnel. The risk of birth defects in children of Gulf War personnel was the same as in the control population (Cowan et al., 1997). This important study, the largest to date on birth defects, was limited to military hospitals and thereby excluded persons ineligible for care in military hospitals (members of the National Guard, reserves, and those who left the military over the course of study). National Guard and reserve troops, as noted earlier, constituted a relatively high percentage of US troops deployed to the Gulf War (Table A.1). Anecdotal reports of an excess of Goldenhar syndrome, a rare congenital anomaly that affects the development of facial structures, prompted another study of birth defects. The syndrome is not specifically coded for in reporting birth defects, so the study reviewed medical records of all listings in several more inclusive birth defect categories that would have subsumed it. Araneta and colleagues (1997) found too few cases of Goldenhar syndrome from which to draw definitive conclusions.

The recently published population-based VA study of US Gulf War veterans found that male veterans reported a significantly higher rate of miscarriage than did controls, and both male and female veterans reported significantly higher birth defects among liveborn infants. Concerned about reporting bias, the investigators suggested that the observation needs to be confirmed by a review of medical records (Kang et al., 2001).

Several ongoing studies are addressing the limitations of previous studies. Population-based studies to capture births in all hospitals—both military and civilian—are under way in the United States and the UK. A large US study will pool birth-defect data from several states by matching statewide birth certificates with military records (Araneta et

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al., 1999). Another UK study is probing the prevalence of birth defects, problems in reproduction and fertility, and cancer in children; this study covers all UK Gulf War veterans and Gulf War-era controls, a total of 106,000 veterans (Doyle et al., 1999).

Studies of Stress-Related Disorders

Two population-based epidemiologic studies of Gulf War veterans described earlier detected a significant increase in the self-reported prevalence of symptoms of PTSD and depression (Goss Gilroy Inc., 1998; Iowa Persian Gulf Study Group, 1997).[22] In the Iowa study, 17% of Gulf War veterans reported symptoms of depression and 1.9% reported symptoms of PTSD.[23] Those figures were significantly higher than those for nondeployed controls, whose prevalences were 11% and 0.8%, respectively (Table A.4). The third population-based study found that UK Gulf War veterans were about 2.5 times more likely than controls to have symptoms of PTSD; there were no significant differences in the levels of depression between deployed veterans and controls (Unwin et al., 1999). The large, population-based VA study did not survey veterans for PTSD or depression (either symptoms or diagnoses).

The rates of PTSD and depression in less-representative military units also have been studied. In a study of military personnel (n = 16,167) from Pennsylvania and Hawaii (described earlier), 8–9% of deployed veterans met criteria for PTSD symptoms on the basis of self-reported symptom checklists compared with 1–2% of nondeployed veterans (Stretch et al., 1996). Similarly, a small study found higher PTSD scores in deployed than in nondeployed veterans (Perconte et al., 1993a).

Sutker and colleagues (1993) compared 215 National Guard and Army reserve veterans who were deployed to the Gulf War with 60 veterans from the same unit who were activated but not deployed overseas. None had sought mental health treatment. The investigators found that 16–24% of war zone-exposed troops had symptoms of distress that suggested depression or PTSD. Those who reported higher levels of stress had greater severity of PTSD and more health complaints than veterans who had low self-reported stress or no war-zone stress. Similarly, PTSD symptoms or diagnoses were more likely in groups of Gulf War veterans who had combat exposure or injury (Baker et al., 1997; Labbate et al., 1998; Wolfe et al., 1998), in women (Wolfe et al., 1993), in veterans who had been exposed to missile attack (Perconte et al., 1993b), and in those who had grave-registration duties (Sutker et al., 1994).

A study by Engel and colleagues (1999) is one of the few that used a clinician-administered diagnostic instrument rather than self-reported symptom scales to assess the presence of psychiatric disorders. Researchers compiled diagnoses from among all Gulf War veterans (n = 13,161) who sought health examinations through the DOD registry during its first year of operation (1994–1995). The authors used the *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III-R [SCID-NP]) to explore a range of possible psychiatric disorders and the Clinician-

[22]Most epidemiologic studies of veterans have assessed the prevalence of self-reported symptoms of PTSD by asking subjects to fill out validated psychometric scales, such as the Mississippi Scale for Combat-Related PTSD and the PTSD Checklist—Military. Psychometric scales of PTSD, useful as screening tools for approximating a PTSD diagnosis, are not deemed to be diagnostic by themselves (Keane et al., 1988; Kulka et al., 1991).

[23]A recent reanalysis of PTSD-symptom prevalence in the Iowa cohort found an adjusted OR of 2.02 for deployed versus nondeployed veterans, but the finding was of borderline significance (confidence interval, 0.97-4.23) (Barrett et al., 2002).

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Administered PTSD Scale to explore PTSD. Both measures have been psychometrically validated on combat veterans, so this study is methodologically stronger than many of the previous investigations. However, the study did not use a control or comparison group and, in using a treatment-seeking population, was not, by design, representative of the Gulf War veteran population. The authors found that 37% of the veterans met criteria for at least one psychiatric disorder. About 13% of the entire sample met diagnostic criteria for mood disorders, 14% for somatoform disorders,[24] and 6% for current PTSD. A study of a subset of this cohort (n = 131) referred for specialty evaluation found that PTSD and somatoform disorders were associated with the reporting of traumatic events (such as handling dead bodies) (Labbate et al., 1998). The authors of the smaller study concluded that at least some veterans with unexplained physical symptoms might be suffering the consequences of combat trauma.

There is only one longitudinal study of PTSD in Gulf War veterans. The rates of PTSD symptoms, measured with a validated symptom questionnaire known as the Mississippi Scale for Combat-Related PTSD, showed an increase from 3% of deployed veterans immediately after the war to 8% in 1993–1994 (Wolfe et al., 1999). Women and veterans with the highest levels of combat exposure were at greatest risk for PTSD. Two years later, in 1994–1996, the same research team conducted an even more methodologically rigorous study via structured clinical interviews (in addition to PTSD questionnaires). They found a current diagnosis of PTSD in 5–7% of deployed veterans (n = 206) compared with none in a control group deployed to Germany (n = 48) (Wolfe et al., 1999). Regarding depression, the 1994–1996 wave of the study found similarly increased rates of current major depressive disorder and dysthymia (two distinct types of depression) but did not find increased rates of somatoform disorders. Yet nearly two-thirds of veterans who reported health symptoms in the moderate to high range had no current psychiatric diagnosis, such as PTSD or major depressive disorder.[25] The authors concluded that although psychiatric diagnosis is associated with some Gulf War health complaints, such diagnoses do not account entirely for the full range and extent of Gulf War veterans' symptom reporting.

Studies of Infectious Disease, Gastrointestinal Symptoms, and Testicular Cancer

During the Gulf War, the occurrence of infectious diseases was lower than expected (Hyams et al., 1995). The most common infectious disease among US troops was diarrheal disease caused by the bacterial pathogens *Escherichia coli* and *Shigella sonnei*, as detected by stool cultures (Hyams et al., 1991). Almost 60% of troops who responded to a questionnaire reported at least one episode of diarrheal disease within an average of 2 months in Saudi Arabia (Hyams et al., 1991). Upper respiratory infections also were frequent (Hyams et al., 1995). Finally, 19 cases of cutaneous leishmaniasis and 12 cases of a variant of visceral leishmaniasis have been reported among US Gulf War veterans.[26] The latter is an unusual finding because the etiologic agent found in veterans' tissue samples—

[24]This term encompasses a variety of disorders in which patients have multiple physical symptoms that are not explained by a known medical disease or condition, by the effects of a substance, or by another mental disorder. The symptoms cause clinically significant distress or impaired functioning (APA, 1994).
[25]About 40% also had no lifetime history of these disorders (Wolfe et al., 1999).
[26]Leishmaniasis is a variety of diseases affecting the skin (cutaneous leishmaniasis), mucous membranes, and internal organs (visceral leishmaniasis), caused by infection with single-celled parasites of the genus Leishmania. It is transmitted from infected animals or people to new hosts by the bites of sand flies (Clayman, 1989).

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the protozoan parasite *Leishmania tropica,* transmitted by sand flies—is not endemic to the Persian Gulf area and is usually associated with cutaneous leishmaniasis (CDC, 1992; Hyams et al., 1995; Magill et al., 1993). Because veterans' symptoms (such as fever, lymphadenopathy, and hepatosplenomegaly) were milder than symptoms of classic visceral leishmaniasis, the condition was given the name viscerotropic leishmaniasis. Even though visceral leishmaniasis and its variants are chronic infectious diseases, the cases were considered too few and classic signs and symptoms too readily detectable at physical examination to account for the much more frequent occurrence of unexplained illnesses in veterans (Hyams et al., 1995; PAC, 1996). Furthermore, in the controlled study of Gulf War veterans by Fukuda and colleagues (1998), none of the eight participants who seroreacted to leishmanial antigens met the study's case definition of a severe case of unexplained illness; that suggests that viscerotropic leishmaniasis is distinct from veterans' unexplained illnesses. However, some people with visceral or viscerotropic leishmaniasis can present with nonspecific symptoms (fatigue, low-grade fever, and gastrointestinal symptoms) that are consistent with those seen in veterans who have unexplained illnesses. Further research is required (NIH, 1994).

Gastrointestinal complaints, as noted earlier, are somewhat common among veterans in the DOD and VA registries (Joseph, 1997; Murphy et al., 1999, Table A.2). In the study noted earlier by Proctor and colleagues (1998), gastrointestinal symptoms were among the symptoms with greatest prevalence differences between deployed and nondeployed veterans. One study investigated a host of gastrointestinal symptoms in a National Guard unit (n = 136). Excessive gas, loose stool, incomplete rectal evacuation, and abdominal pain were more prevalent during and after the war in deployed than in nondeployed veterans from the same unit (Sostek et al., 1996). The results were based on a 64-item questionnaire administered after the war. Subjects reported that their gastrointestinal complaints began while in the Persian Gulf area and persisted after return to the United States. A population-based study of Danish peacekeeping troops who were sent to the Persian Gulf after the war had significantly higher prevalence of gastrointestinal symptoms among deployed (9.1%) than nondeployed (1.7%) veterans (Ishoy et al., 1999a). The population-based study of US veterans found up to 25% of veterans reporting medical conditions of gastritis and frequent diarrhea (Kang et al., 2000, Table A.6).

Over the last 5 months of 1991, hospitalizations for testicular cancer were slightly increased in a large study of active-duty deployed versus nondeployed veterans (Gray et al., 1996). In a followup study, the investigators extended their analysis through 1996. They replicated their earlier finding but found that by 4 years after the war the cumulative risk of testicular cancer was similar in the two groups of veterans (Knoke et al., 1998). They attributed the transient increase in testicular cancer immediately after the war to regression to the mean because of the healthy-soldier effect and to deferral of care during deployment (during which time they would not have had the opportunity for diagnosis and treatment).

LIMITATIONS OF PAST AND CURRENT STUDIES

The epidemiologic studies of Gulf War veterans summarized above have contributed greatly to our understanding of veterans' symptoms, but they are beset by limitations commonly encountered in epidemiologic studies. A major limitation is representativeness;

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most studies focus on groups that are not representative of all Gulf War veterans with respect to their military duties and location during deployment, their military status during the war (active duty, reserves, or National Guard), their military status after the war (active duty, reserves, or discharged), their branch of service (Army, Navy, Air Force, or Marines), or ease of ascertainment (IOM, 1999a). The VA study, with its population-based design, is the most representative of US veterans. The findings of population-based studies in Canada (Goss Gilroy Inc., 1998) and the UK (Unwin et al., 1999; Cherry et al., 2001a) are generally consistent with the VA and other large US studies.

Other limitations of epidemiologic studies include small samples, low participation rates that could result in selection bias in some studies, and recall bias.[27] The potential for recall bias is particularly important because most studies rely on self-reporting of symptoms and exposures years after the event rather than on biologic measures (Joellenbeck et al., 1998). Veterans with more symptoms are more likely to report more exposures (Unwin et al., 1999). Outcome misclassification is also a concern. One study found disparities between veterans' symptom reporting on questionnaires and later clinical examination (McCauley et al., 1999). Studies might also be too narrow in their assessment of health status. The measurement instruments might have been too insensitive to detect abnormalities that affect deployed veterans. Finally, the period of investigation has, of necessity, been too brief to detect health outcomes that have a long latency or require many years to progress to the point where disability, hospitalization, or death occurs. Virtually all US studies are cross-sectional, and this limits the opportunity to learn about symptom duration and chronicity, latency of onset (especially for health conditions with a long latency, such as cancer), and prognosis.

A major problem for most epidemiologic studies of Gulf War veterans is the lack of biologic measures of exposure to potentially harmful agents. Reliance on self-reported exposures, which often took place years earlier, lacks external verification and is subject to recall bias, a problem that potentially affects many retrospective epidemiologic studies. Furthermore, self-reports of exposure may be complicated by recall of perceived—rather than actual—exposures (for example, because of the sensitivity of the monitors, many false alarms may have been perceived as chemical-warfare agent exposure). Enhanced record keeping and monitoring of the environment during and after the Gulf War would have averted this problem. Indeed, many expert panels have recommended efforts to improve record-keeping and environmental monitoring in future deployments (e.g., IOM, 1999b; NRC, 2000a,b,c).

CONCLUSION

This appendix provides an overview of the body of published studies on the health of Gulf War veterans. Gulf War veterans report more symptoms than do their nondeployed counterparts, according to methodologically robust studies from several countries (Goss Gilroy Inc., 1998; Kang et al., 2000; Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999). Symptoms related to cognition, the musculoskeletal system, and fatigue are more prevalent among Gulf War veterans than controls. Many symptoms and their clustering do

[27]Selection bias would occur if Gulf War veterans who were symptomatic chose to participate in a study more frequently than those who were not symptomatic. Recall bias would occur if Gulf War veterans who were symptomatic tended to overestimate their exposures compared with veterans who were not symptomatic.

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not appear to fit conventional diagnoses. The question is whether these unexplained symptoms constitute a syndrome and, if so, whether they are best studied and treated as a unique new syndrome or as a variant form of an existing syndrome (IOM, 2000). Although one uncontrolled study reported several unique new syndromes through factor analysis (Haley et al., 1997), four controlled studies did not uncover a unique syndrome (Doebbeling et al., 2000; Fukuda et al., 1998; Ismail et al., 1999; Knoke et al., 2000). Since then, a new factor analysis study has been reported by the VA on a population-based sample of Gulf War deployed versus nondeployed veterans (Kang et al., 2002). The authors found a unique neurologic factor marked by dizziness/balance-related symptoms. They interpreted their findings as suggesting a possible syndrome related to Gulf War deployment that requires objective supporting clinical evidence.

The very lack of definition or classification of veterans' unexplained symptoms and illnesses has made it difficult to diagnose and treat many Gulf War veterans (IOM, 2001). The commonality of the symptoms in the general population (Kroenke and Mangelsdorff, 1989), coupled with their nonspecific nature and lack of biologic markers, has made it difficult to determine which, if any, exposures or sets of exposures during the Gulf War are responsible.

The health studies reviewed in this appendix have found little or no excess mortality, hospitalizations, or birth defects in the children of veterans, although the studies have some limitations. Deployment to the Gulf War is associated with stress-related disorders, such as PTSD and depression, but a sizable number of veterans with unexplained symptoms do not have any psychiatric diagnoses.

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B

CONCLUSIONS AND RECOMMENDATIONS: GULF WAR AND HEALTH, VOLUME 1

The conclusions and research recommendations of the IOM report *Gulf War and Health, Volume 1, Literature Review of Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines* are provided below.

CONCLUSIONS

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that a causal relationship exists between the exposure to a specific agent and a health outcome in humans. The evidence fulfills the criteria for sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biological plausibility.

Exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months.

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between an exposure to a specific agent and a health outcome in human studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

- Pyridostigmine bromide and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes.
- Anthrax vaccination and transient acute local and systemic effects.
- Botulinum toxoid vaccination and transient acute local and systemic effects.

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Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between exposure to a specific agent and a health outcome in humans, but is limited because chance, bias, and confounding could not be ruled out with confidence.

- Exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects.

Inadequate/Insufficient Evidence to Determine Whether an Association Does or Does Not Exist

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure to a specific agent and a health outcome in humans.

- Exposure to uranium and lung cancer at higher levels of cumulative exposure (>200 mSv or 25 cGy).
- Exposure to uranium and lymphatic cancer; bone cancer; nervous system disease; nonmalignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on hematological parameters, reproductive or developmental dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects, or musculoskeletal effects).
- Pyridostigmine bromide and long-term adverse health effects.
- Exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse health effects.
- Anthrax vaccination and long-term adverse health effects.
- Botulinum toxoid vaccination and long-term adverse health effects.
- Multiple vaccinations and long-term adverse health effects.

Limited/Suggestive Evidence of No Association

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, that are mutually consistent in not showing a positive association between exposure to a specific agent and a health outcome at any level of exposure. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

- Exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy.
- Exposure to uranium and clinically significant renal dysfunction.

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RESEARCH RECOMMENDATIONS

Biological, Chemical, and Psychological Interactions

- Research on the interactions among the multiple agents and stressors to which military personnel were exposed as a result of the Gulf War conflict.

Depleted Uranium

- Continued followup of the Baltimore cohort of Gulf War veterans with DU exposure. Long-term studies of the health of other Gulf War veterans at high risk for DU exposure (e.g., cleanup or radiation control units).
- Continued followup of the cohorts of uranium processing workers.
- Additional studies of the effects of DU in animals.

Sarin

- Long-term followup of populations exposed to sarin in the Matsumoto and Tokyo terrorist attacks.
- Studies in experimental animals to investigate the long-term effects of an acute, short-term exposure to sarin at doses that do not cause overt cholinergic effects and minimal acetylcholinesterase inhibition.
- Research on genetic factors that may alter susceptibility to sarin toxicity.

Pyridostigmine Bromide

- Research on chemical interactions between PB and other agents such as stress, and certain insecticides.
- Research on genetic factors (e.g., genetic polymorphisms of butyrylcholinesterase, paraoxonase) that may alter susceptibility to the effects of PB.
- Epidemiologic studies on the possible long-term health effects of PB.

Vaccines

- Long-term longitudinal studies of participants in the Anthrax Vaccine Immunization Program that would actively monitor and systematically collect and analyze data about symptoms, functional status, and disease status.
- Long-term systematic research to examine potential adverse effects of anthrax and botulinum toxoid vaccination in multiple species and strains of animals.
- Careful study of current symptoms, functional status, and disease status in cohorts of Gulf War veterans and Gulf War-era veterans for whom vaccination records exist.

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C

IDENTIFYING THE LITERATURE

This appendix is a brief overview of the approach used by the Institute of Medicine committee and staff in identifying the scientific and medical literature that would form the basis of the committee's review. It is not meant to be a comprehensive guide to searching the insecticide and solvent literature.

LITERATURE SEARCHES

Online Databases

Online databases were used extensively to identify the relevant peer-reviewed literature. Most of the literature searches were conducted in medical and scientific bibliographic databases available through Dialog, a commercial vendor of over 470 databases that cover a wide array of disciplines. From Dialog's catalog of databases, staff chose the ones that contained peer-reviewed scientific literature in the biomedical sciences and in environmental and occupational health, public health, toxicology, biology, and chemistry (Table C.1). There was subject and content overlap, but each database has a unique subject emphasis and indexes literature not available elsewhere. Given the study's focus on long-term human health effects of insecticides and solvents, MEDLINE and EMBASE were particularly useful because of their extensive coverage of US and international scientific and biomedical journals. MEDLINE is produced by the US National Library of Medicine and covers over 4300 journals published throughout the world. The database provides coverage from 1966 to the present and contains over 11 million citations. EMBASE, produced by Elsevier Science, indexes over 3300 primary journals with a focus on the international literature. EMBASE indexes journal articles from 1974 to the present and contains over 8 million citations. Both databases add about 40,000 records each year. To provide essential toxicologic and chemical information on each of the insecticides and solvents, factual databases (Table C.2) were searched. Together, the bibliographic and factual databases offer the most effective means of identifying the international peer-reviewed scientific literature published since the middle 1960s. Other strategies were used to identify literature published before then (see "Other Sources" below).

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TABLE C.1 Bibliographic Databases

Name	Producer	Coverage	Size
BIOSIS Previews	BIOSIS	1969 to present	Over 12,257,000 records (as of May 2000)
CAB HEALTH	CAB International	1973 to present	616,000 records (as of Dec 1997)
CANCERLIT	US National Cancer Institute	1975 to present	Over 1,693,000 records (as of Aug. 2001)
EMBASE	Elsevier Science BV	1974 to present	Over 8,052,000 records (as of Apr. 2000)
Environmental Bibliography	Environmental Studies Institute	1973 to present	Over 590,000 records (as of March 1998)
Life Sciences Collection	Cambridge Scientific Abstracts	1982 to present	Over 1,600,000 records (as of Dec. 1997)
MEDLINE	US National Library of Medicine	1966 to present	Over 11,149,899 records (as of Sept. 2001)
National Technical Information Service	US Department of Commerce	1964 to present	Over 2,112,000 records (as of May 2000)
Occupational Safety and Health	National Institute for Occupational Safety and Health	1973–1998	210,155 records (file closed)
PsycINFO	American Psychological Association	1887 to present	Over 1,688,000 records (as of Dec. 2000)
Science Citation Index	Institute for Scientific Information – Thomson Scientific	1975 to present	Over 10,048,000 records (as of Oct. 2001)
TOXLINE	US National Library of Medicine	1965 to present	2,400,00 records (as of Feb. 1998)
WorldCat	OCLC Online Computer Library Center, Inc	Unlimited	Over 46,000,000 cataloging records

TABLE C.2 Factual Databases

ChemID Plus
Extension Toxicology Network (EXTOXNET)
Hazardous Substances Data Bank (HSDB)
Integrated Risk Information System (IRIS)

Dialog's robust search engine allows the use of complex search strategies in multiple databases simultaneously. However, databases often contain unique fields of data or use different indexing systems. For example, the records of BIOSIS and CAB HEALTH include Chemical Abstract Service (CAS) registry numbers; other databases do not include CAS registry numbers as a data element but instead rely on chemical names and synonyms. All search strategies were designed to capture relevant CAS registry numbers wherever available but with the recognition that databases lacking CAS registry numbers would not be as well represented in the retrieval set and that additional searching was needed.

Another challenge in conducting relevant and comprehensive literature searches is the diversity of indexing systems used by database producers. For example, MEDLINE, EMBASE, and PsycINFO are professionally indexed with a controlled set of vocabulary terms or subject codes; using MEDLINE's index term *carbaryl* automatically retrieves all studies that use the term *carbaryl* and ones that use the alternative spelling *carbaril* or the trade name *Sevin*. By using the controlled thesaurus terms, staff could be certain that all synonyms, alternative spellings, trade names, and equivalent conceptual terms were automatically retrieved in the search results. Other databases, however, do not use a controlled vocabulary but instead rely on author-assigned index terms. To address that problem, search strategies were expanded to include specifically not only the standard

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insecticide and solvent terms but also other spelling variations, synonyms, and commercial names. Thus, a series of search strategies were developed to take advantage of the classification scheme, controlled vocabulary, and distinct structure of each database.

In addition to the complexities presented by the databases, the literature on the insecticides and solvents being reviewed in this study afforded its own set of challenges as committee members and staff worked to identify the pertinent literature comprehensively while minimizing the retrieval of nonrelevant citations. For instance, ethylene glycol and butyl acetate, two solvents under study, are referred to in numerous articles that describe laboratory procedures but not human health effects. Searching for the solvent ethanol was confounded by the retrieval of numerous articles on alcoholism. Similarly, many efficacy and treatment-related studies, such as those of the effectiveness of various insecticides on mosquito nets or evaluating treatment options for head lice, were retrieved by a search for malathion and permethrin. It is not always possible to design a comprehensive search strategy that retrieves the citations needed for the committee's purposes but eliminates all citations that are not useful to the committee.

The search for insecticides included the 11 insecticides listed in the congressional legislation and three additional insecticides (d-phenothrin, azamethiphos, and bendiocarb) identified by the Office of the Special Assistant for Gulf War Illnesses as having been used by military personnel during the Gulf War. The search for solvents included the 53 specific solvents that were sent to the Gulf War as determined by the Department of Defense's Defense Logistics Agency.

Although the search strategies varied somewhat with their purpose and the structure of the databases being searched, the foundation of every major search contained the same basic elements: specific insecticides and solvents, their synonyms, alternative spellings, trade names, CAS registry numbers, insecticide and solvent classes (such as organophosphates, carbamates, acetates, and glycols), and the general terms *pesticides, insecticides*, and *solvents*. All databases were searched in their entirety, and all foreign-language citations were retained; any studies that the committee deemed significant were translated into English.

Because the focus of the committee's work was to review the literature regarding the human health effects of insecticide and solvent exposure, the primary searches used the comprehensive search strategy discussed above and then limited the retrieval to human studies. For some database searches, terms like *adverse effects*, e*pidemiologic study*, *controlled study*, and *cohort* were added to the search strategies. Nearly 30,000 citations were initially identified and reviewed for their relevance to the committee. However, as discussed above, because of the attempt to be as comprehensive as possible, the search strategies retrieved many references that were not relevant for the committee's purposes.

A second goal of the literature search was to provide the committee with a broad overview of the toxicology of insecticides and solvents so that it could assess biologic plausibility. Textbooks and reports, such as the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, provided much of the background material, but online bibliographic databases were used to identify the current literature and review articles.

Throughout the study, smaller targeted searches were conducted on specific topics, such as insecticide and solvent interactions, occupational exposures, and inert ingredients found in insecticide and solvent formulations. The secondary searches were especially

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useful for double-checking the thoroughness of the primary search strategies. In addition, the primary and secondary searches combined yielded many pertinent case reports, background, and review articles that were retained for use as supporting material as needed by the committee.

To ensure that the committee reviewed the complete body of evidence before forming its conclusions, searches were conducted through August 2001.

Other Sources

Identifying the pertinent literature was a continuing process throughout the study. In addition to the formal online searches, the committee and staff examined the reference lists of major epidemiologic studies, review articles, and textbooks for relevant citations. The bibliographies of such reports as the International Agency for Research on Cancer's monograph series, ATSDR's Toxicological Profiles, the World Health Organization's Environmental Health Criteria documents, and the technical reports of the European Centre for Ecotoxicology and Toxicology of Chemicals provided many relevant citations. Online library catalogs, including those of the US National Library of Medicine and the National Institutes of Health, were searched for textbooks and other monographs that could provide pertinent overview and background materials for the study.

MANAGING THE INFORMATION

The results of the online searches and citations identified by other means were imported into ProCite, a software program designed to store and manage bibliographic data. When the search phase was completed, ProCite contained nearly 30,000 citations that included all the relevant and nonrelevant epidemiologic and toxicologic studies, background reports, and other articles. Staff reviewed each citation carefully and identified about 3000 citations as most relevant to the committee's charge. The citations selected were studies of human populations exposed to the agents of interest that examined the potential for adverse health effects. The full text of those journal articles was retrieved and sent to committee members for their review.

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D

INSECTICIDES AND SOLVENTS SENT TO THE GULF WAR

Insecticides

Chlorpyrifos	Propoxur
Diazinon	Methomyl
Malathion	Lindane
Dichlorvos	Permethrin
Azamethiphos	d-Phenothrin
Carbaryl	DEET[b]
Bendiocarb	

[a]Noted as proxpur in Congressional Legislation, PL 105–277 and PL 105–368.
[b]*N,N*-Diethyl-3-methylbenzamide or *N,N*-diethyl-*m*-toluamide. DEET is an insect repellent.

Solvents

Acetic acid	Isopentyl alcohol
Acetone	Isopropyl alcohol
Amyl acetate	Methanol
Benzene	1-Methoxy-2-propanol acetate
2-Butoxyethanol (ethylene glycol monobutyl ether)	Methylene chloride (dichloromethane)
Butyl acetate	Methyl ethyl ketone
Butyl alcohol	Methyl isoamyl ketone
Camphor	Methyl isobutyl ketone
Chloroform	Methyl propyl ketone
Cresol	Morpholine
Cresylic acid	Naphtha (petroleum ether)
Cyclohexanol	Phenol
Cyclohexanone	Polyalkylene glycol
Dichlorodifluromethane	Potassium hydroxide
Diethylene glycol	Propylene glycol
Diethylene glycol monobutyl ether	Stoddard solvent
Diethylene triamine	Tetrachloroethylene
Dipropylene glycol	Toluene
Ethanol	1,1,1-Trichloroethylene
Ethyl acetate	1,1,2-Trichloro-1,2,2-trifluoroethane
2-Ethyl butanol	Trichloroethyleve
Ethylene glycol	Tricresyl phosphate
Ethylene glycol monoethyl ether	Xylene
Ethylene glycol monomethyl ether	
Ethyl ether	
Glycerol	
n-Heptane	
Hexyl alcohol	
Hexylene glycol	
Isoamyl acetate	

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E

RELATIVE RISKS FOR LUNG CANCER

Table E.1 shows detailed results[1] under certain assumptions of the prevalence of smoking in the general population and in the occupational cohort. Some of the scenarios are rather implausible, for example, assuming that 70% of the population is heavy smokers. In cases where the prevalence of smoking in the general population exceeds that of the cohort, the expected relative risks are less than unity, meaning that an observed excess relative risk in the cohort would be underestimated because of confounding by smoking. Expected relative risks greater than unity, as would occur when there are more and heavier smokers in the occupational cohort, are interpreted as meaning that some of an observed effect could be explained by smoking. In the instance where all cohort members smoke heavily, the maximum relative risk that could be observed is 3.1. In general, the table shows that one requires extreme differential smoking patterns to explain observed relative risks above 1.5.

The expected relative risks for lung cancer due solely to smoking presented below. Table E.1 was calculated assuming a relative risk for "moderate" smoking of 10 and for "heavy" smoking of 20.

TABLE E.1 Relative Risks for Lung Cancer

General Population 40% Moderate and 10% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	1.0
50	10	1.1
60	10	1.3
70	10	1.4
30	20	1.2
40	20	1.3
50	20	1.4
60	20	1.6
20	30	1.3
30	30	1.4
40	30	1.6
50	30	1.7
10	40	1.5
10	50	1.8
10	60	2.0
10	70	2.3

General Population 50% Moderate and 10% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.9
50	10	1.0
60	10	1.1
70	10	1.2
30	20	1.0
40	20	1.1
50	20	1.3
60	20	1.4
20	30	1.1
30	30	1.3
40	30	1.4
50	30	1.5
10	40	1.3
10	50	1.5
10	60	1.8
10	70	2.1

General Population 60% Moderate and 10% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.8
50	10	0.9
60	10	1.0
70	10	1.1
30	20	0.9
40	20	1.0
50	20	1.1
60	20	1.2
20	30	1.0
30	30	1.1
40	30	1.2
50	30	1.3
10	40	1.1
10	50	1.4
10	60	1.6
10	70	1.8

[1]Provided by Mark Goldberg, Ph.D.

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(TABLE E.1 cont)

General Population 70% Moderate and 10% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.7
50	10	0.8
60	10	0.9
70	10	1.0
30	20	0.8
40	20	0.9
50	20	1.0
60	20	1.1
20	30	0.9
30	30	1.0
40	30	1.1
50	30	1.2
10	40	1.0
10	50	1.2
10	60	1.4
10	70	1.7

General Population 30% Moderate and 20% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.9
50	10	1.0
60	10	1.1
70	10	1.2
30	20	1.0
40	20	1.1
50	20	1.2
60	20	1.4
20	30	1.1
30	30	1.3
40	30	1.4
50	30	1.5
10	40	1.3
10	50	1.5
10	60	1.8
10	70	2.0

General Population 40% Moderate and 20% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.8
50	10	0.9
60	10	1.0
70	10	1.1
30	20	0.9
40	20	1.0
50	20	1.1
60	20	1.2
20	30	1.0
30	30	1.1
40	30	1.2
50	30	1.3
10	40	1.1
10	50	1.4
10	60	1.6
10	70	1.8

General Population 50% Moderate and 20% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.7
50	10	0.8
60	10	0.9
70	10	1.0
30	20	0.8
40	20	0.9
50	20	1.0
60	20	1.1
20	30	0.9
30	30	1.0
40	30	1.1
50	30	1.2
10	40	1.0
10	50	1.2
10	60	1.4
10	70	1.6

General Population 60% Moderate and 20% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.6
50	10	0.7
60	10	0.8
70	10	0.9
30	20	0.7
40	20	0.8
50	20	0.9
60	20	1.0
20	30	0.8
30	30	0.9
40	30	1.0
50	30	1.1
10	40	0.9
10	50	1.1
10	60	1.3
10	70	1.5

General Population 20% Moderate and 30% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.8
50	10	0.9
60	10	1.0
70	10	1.1
30	20	0.9
40	20	1.0
50	20	1.1
60	20	1.2
20	30	1.0
30	30	1.1
40	30	1.2
50	30	1.3
10	40	1.1
10	50	1.3
10	60	1.6
10	70	1.8

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(TABLE E.1 cont)

General Population 30% Moderate and 30% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.7
50	10	0.8
60	10	0.9
70	10	1.0
30	20	0.8
40	20	0.9
50	20	1.0
60	20	1.1
20	30	0.9
30	30	1.0
40	30	1.1
50	30	1.2
10	40	1.0
10	50	1.2
10	60	1.4
10	70	1.6

General Population 40% Moderate and 30% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.6
50	10	0.7
60	10	0.8
70	10	0.9
30	20	0.7
40	20	0.8
50	20	0.9
60	20	1.0
20	30	0.8
30	30	0.9
40	30	1.0
50	30	1.1
10	40	0.9
10	50	1.1
10	60	1.3
10	70	1.5

General Population 50% Moderate and 30% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.6
50	10	0.7
60	10	0.7
70	10	0.8
30	20	0.7
40	20	0.8
50	20	0.8
60	20	0.9
20	30	0.8
30	30	0.8
40	30	0.9
50	30	1.0
10	40	0.8
10	50	1.0
10	60	1.2
10	70	1.4

General Population 10% Moderate and 40% Heavy		
Moderate (RR=10)	Heavy (RR=20	Expected RR
40	10	0.7
50	10	0.8
60	10	0.9
70	10	1.0
30	20	0.8
40	20	0.9
50	20	1.0
60	20	1.1
20	30	0.9
30	30	1.0
40	30	1.1
50	30	1.2
10	40	1.0
10	50	1.2
10	60	1.4
10	70	1.6

General Population 10% Moderate and 50% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.6
50	10	0.6
60	10	0.7
70	10	0.8
30	20	0.7
40	20	0.7
50	20	0.8
60	20	0.9
20	30	0.7
30	30	0.8
40	30	0.9
50	30	1.0
10	40	0.8
10	50	1.0
10	60	1.2
10	70	1.3

General Population 10% Moderate and 60% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.5
50	10	0.6
60	10	0.6
70	10	0.7
30	20	0.6
40	20	0.6
50	20	0.7
60	20	0.8
20	30	0.6
30	30	0.7
40	30	0.8
50	30	0.8
10	40	0.7
10	50	0.9
10	60	1.0
10	70	1.1

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(TABLE E.1 cont)

General Population 10% Moderate and 70% Heavy		
Moderate (RR=10)	Heavy (RR=20)	Expected RR
40	10	0.4
50	10	0.5
60	10	0.5
70	10	0.6
30	20	0.5
40	20	0.6
50	20	0.6
60	20	0.7
20	30	0.6
30	30	0.6
40	30	0.7
50	30	0.7
10	40	0.6
10	50	0.8
10	60	0.9
10	70	1.0

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F

NEUROLOGIC EXAMINATION

The neurologic examination includes a complete patient history and assessment by a clinician of a patient's mental status, cranial nerve function, motor control, strength, posture, gait, and the functioning of sensory and reflex pathways. The history is important for determining potential sources of occupational or environmental exposures that might be associated with symptoms and clinical findings. Specific symptoms and signs—such as motor weakness, incoordination, sensory loss and altered mental status—arise from abnormalities in the functioning of the specialized cells of the brain, spinal cord, and peripheral nerves.

This appendix covers the neurologic examination and, more specifically, testing for three of the neurologic outcomes discussed in Chapter 7: peripheral neuropathy, neurobehavioral effects, and sensory effects. The tests described are not limited to neurotoxicology; they also apply to the study of neurologic diseases and psychiatric disorders.

TESTING FOR AND DIAGNOSIS OF PERIPHERAL NEUROPATHY

Peripheral neuropathy is a general term referring to any abnormality, inflammation, or disease of a peripheral nerve. Diabetes and alcoholism are the most common causes of peripheral neuropathy (Poncelet, 1998). Exposure to neurotoxins, including heavy metals, also can cause peripheral neuropathy. Most peripheral neuropathies from neurotoxins present as a pattern of distal symmetric signs and symptoms, that is, a dying-back process starting in the tips of the toes and progressing proximally in a stocking-glove distribution. The two types of underlying pathophysiologies are axon loss and demyelination.

The diagnosis of peripheral neuropathy relies on findings of a clinical neurologic examination, including patterns and time course of signs and symptoms and the exposure history. The findings should be confirmed with quantitative laboratory testing through nerve conduction studies and electromyography.

The most common symptoms and signs of exposure to neurotoxins appear first in sensory and later in motor nerves (Poncelet, 1998). Symptoms of peripheral neuropathy include fatigability, weakness, paresthesia, numbness, spontaneous sensation of burning heat and cold, and pain. Signs include loss of power (e.g., reduced grip strength), and abnormalities in reflexes and sensations (e.g., of vibration, touch, and position). The time course is important, inasmuch as most neurotoxic, nutritional, and systemic causes of

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peripheral neuropathy develop over weeks or months. A slowly progressive course suggests a hereditary or metabolic cause. Nerve conduction and electromyography are used to confirm the diagnosis and to determine the type of pathophysiologic effect, especially whether the neuropathy is demyelinating or axonal.

Measuring nerve conduction is a key method for testing the functioning of a peripheral nerve. Its purpose is to localize where the pathology is along the length of the nerve. It also aids in characterizing the pathology—namely, whether it affects axons, cell bodies, or the myelin sheath (Aminoff, 1987). Testing often involves stimulating a nerve at one point along its path and recording the electrical impulse from the nerve at another point.

Nerve-conduction testing typically measures conduction velocity, expressed as meters/second. Conduction velocity is calculated by dividing the distance between the stimulating and recording points by the time from stimulation to onset of recorded impulse (the latency). Nerve conduction testing also measures the amplitude of the compound action potential of a sensory nerve or the muscular wave (M wave) for a motor nerve. Compound action potential is the sum of individual impulses from axons within the nerve. It is recorded at the surface of a sensory nerve after the nerve has been electrically stimulated. The M wave is the compound action potential recorded from the surface of a muscle after stimulation of a motor nerve. The M wave refers to the sum of individual impulses from axons that control muscular contraction.

If the axon is affected, the amplitude (maximal voltage, in microvolts) of the compound action potential or M wave is generally smaller than normal. Nerve impulses can be conducted only by the remaining undamaged axons and this reduces the magnitude of the compound action potential. If the myelin sheath is affected, the conduction velocity is slower than normal, and other electrophysiological parameters can be affected too.

Nerve conduction studies examine functioning of the peripheral nervous system, and a similar type of testing—known as evoked potentials—is used to examine the functioning of both the peripheral and the central nervous systems. Studies using evoked potentials examine the characteristics of electrical waveforms generated by a stimulus delivered to a sensory receptor or nerve or applied directly to a particular area of the brain, spinal cord, or muscle. There are many types of evoked potentials—including auditory evoked potentials, brainstem auditory evoked potentials, and visual evoked potentials—and each is designed to uncover and localize pathology in distinct parts of the nervous system.

Electromyograms (EMG)

Electromyography (EMG) is used to test motor unit function; a motor unit consists of the motor neuron, its axon, and the muscle cell it innervates. The EMG helps to define the type of neurotoxic insult or neuromuscular disorder.

A typical test uses a recording electrode inserted through the skin into the muscle to measure electrical activity. Thousands of motor units are in the legs. Fewer units are in the head and neck. A reduced number of motor units is evidence of denervation (the loss of connection between the motor neuron, its axon, and the muscle fiber it supplies). Denervation of motor units is necessary before muscle cells begin to develop abnormal, spontaneously discharging potentials. Therefore, the timing of an abnormal electromyogram in relation to a toxic exposure is very important in the interpretation of the results. As toxic neuropathy develops and clinical signs appear, greater EMG changes are recordable. Denervated muscle fibers manifest spontaneous electrical discharges, called fibrillations,

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which can be recorded from a needle electrode inserted into the muscle when it is at rest. Polyphasic potentials are other electrical discharges that can be recorded from a previously denervated muscle that has become reinnervated by adjacent axons.

Vibrotactile Threshold

The vibrotactile threshold, a measure of sensory nerve function, is tested to evaluate the ability to perceive a vibrating stimulus. The test can be performed during a clinical examination with a tuning fork (128 Hz) placed over a toe or finger pad or joint of the foot, ankle, tibia, finger, or wrist. Subjects indicate to the examiner when they feel the vibration or when it diminishes and disappears. Testing can be performed with quantitative standardized methods; this is sometimes referred to as quantitative sensory testing (QST). One commonly used device, known as a Vibratron, assesses the function of large axons (fibers) of a peripheral nerve carrying the sensations of position and vibration. It has a stimulator that delivers vibrations of various amplitudes through two probes applied to the skin over a finger pad or an extremity joint with a constant frequency of vibration (100 Hz). With the so-called forced-choice method (choosing between two alternatives), subjects indicate when they perceive or do not perceive one or both probes vibrating. Testing of an exposed person soon after exposure and later, after removal from exposure, yields evidence of possible impairment and then recovery of vibrotactile sensation perception. Because height and age are known covariates of vibration threshold, epidemiologic studies control for height and age in the analysis and interpretation of results.

NEUROBEHAVIORAL EFFECTS

Neurobehavioral Tests

Neurobehavioral tests (also called neuropsychologic tests) are standardized tests designed to identify functional deficits associated with exposure to neurotoxicants. The tests also help to develop hypotheses about mechanisms of toxicity or localization of affected brain areas.

There are at least 250 distinct neurobehavioral tests, but they can be grouped under distinct domains of mental functioning. No test can be used alone to identify dysfunction as a result of a toxic exposure; rather, many tests are grouped into batteries to provide a broad characterization of a dysfunction (Fiedler et al., 1996). Some standardized test batteries have been developed (such as the WHO Neurobehavioral Core Test Battery and the Halstead-Reitan Battery). The batteries can be administered manually or by computer. Computer-administered tests consume less time and are less expensive to administer. The individual tests in a given battery are known as subtests. Summary scores for subtests in a battery can be used to determine the nature and degree of functional impairment.

One of the most important features of neurobehavioral testing is comprehensiveness of test selection. Given the wide array of tests available, batteries generally should include at least one test from each of the functional domains (Table F.1): overall cognitive ability; attention and concentration; motor skills; visuomotor coordination; visuospatial relations; memory; affect and personality. The functional domains to some extent overlap.

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Testing for overall cognitive ability is important for obtaining a measure of pre-exposure ability. Because standardized indicators of pre-exposure cognitive function are not generally available in study subjects, researchers measuring post-exposure effects often depend on the vocabulary test from the Wechsler Adult Intelligence Scale-Revised to indicate pre-exposure functioning. That approach relies on the assumption that neurotoxicants do not impair performance on well-learned information, such as vocabulary or reading ability.

Other important criteria in test selection and interpretation are a test's psychometric properties (such as standardization and reliability) and its sensitivity to the effects of the neurotoxicant in question. The test should be able to evaluate more than one output performance modality, for example, pushing buttons on a computer and giving verbal responses. A test of a single modality restricts the range of responses available to the subject. For example, spoken tests rely disproportionately on language aptitude and retrieval of information from semantic memory (White and Proctor, 1992; White et al., 1994).

Electroencephalography

Electroencephalography (EEG) provides real-time monitoring of electrophysiological activity of the brain. Electrical activity arising from neurons of the cerebral cortex is recorded from the scalp with electrodes placed on the surface of the skull. Sensitive electronic equipment, which is used to amplify electrical signals, displays patterns of mixed frequencies, amplitudes, and their topographical distributions. The EEG yields predictable patterns in normal waking, drowsing, and sleeping states. Mixtures of high (beta and alpha) and low (theta and delta) frequencies from the frontal, temporal, and occipital lobes are detected. Impairment in brain function, known as encephalopathy, is diagnosed when the EEG symmetry, amplitude, frequencies, and patterns diverge from normal. Spiked discharges indicate sites of epileptic activity. Increased slow-wave activity occurs during exposure to neurotoxicants that depress central nervous system function. The EEG tracing typically returns to a normal pattern after removal from the agent, although behavioral manifestations may persist clinically, or be detectable on further neuropsychologic testing. As with all laboratory tests, the significance of an EEG result depends on its integration with other clinical information and examinations. Electroencephalography is most helpful when an abnormality is chronologically related to exposure to the neurotoxicant.

Posturography

Posturography is used to assess ability to maintain balance. It is more objective than the clinician-administered Romberg test. Maintaining balance is a dynamic process that requires interaction of the peripheral and central nervous systems. Therefore, abnormalities on posturography can suggest central or peripheral dysfunction or both. Quantitative assessment of body sway is accomplished by placing a subject on a multiaxis force platform consisting of two parallel plates with strain gauges that measure and record the changes in pressure associated with the subject's attempt to maintain balance in response to tilting of the platform. Body sway is measured along the lateral and anterior-posterior axis. The test is performed with the subject's eyes open and eyes closed.

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SENSORY EFFECTS

Color Vision Testing

In the Lanthony D-15 test, a subject is shown is a color arrangement consisting of 15 color caps that form a color circle covering the visual spectrum. The subject is asked to select the cap that is closest in hue to a reference cap. The patient places caps in the tray in an orderly transition of hue. The caps are designed so that a person with normal color vision or a mild color-vision deficit will arrange the caps in a perfect color circle. The test does not indicate the degree of color deficiency other than to separate those with normal color vision and mild congenital color blindness from patients with moderate to severe color deficits. It can distinguish significant defects, particularly if a person is screened prior to exposure to a toxicant.

Audiometry

Audiometry measures the ability to discriminate pure tones (500, 1000, 2000, 4000, 6000, and 8000 Hz) presented at 5-dB intervals through a headset. The test takes about 10 minutes to complete and requires concentration on the part of the subjects to distinguish between tones just above and just below the threshold of detection. In the early stages, exposure selectively affects the ability to detect high-frequency sounds (4000, 6000, and 8000 Hz). After continuing exposure, speech frequency sounds (500–2000 Hz) may also be affected.

Audiometry can distinguish between sensorineural hearing loss and hearing loss due to middle ear infections or central nervous system lesions by incorporating additional tests, including measurement of bone conduction, audio evoked potentials, and immittance. Testing of the latter includes acoustic-reflex testing (based on reflex tightening of the tympanic membrane by the stapedius muscle after presentation of an auditory signal and measured by changes in tympanic membrane impedance) and evaluation of decay in the acoustic reflex (associated with central nervous system lesions).

The acoustic reflex threshold is established by using an ascending and descending 5-dB increment-bracketing procedure to determine the minimal intensity required for person to note a change in middle ear compliance. An abnormal reflex decay occurs when a stimulus is present at 10 dB above the reflex threshold, and the amplitude of the reflex decreases to less than half its original value in 10 seconds or less. The main objective in performing immittance measurements is to obtain information on the site of lesions by investigating acoustic reflex findings.

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TABLE F.1 Neurobehavioral Tests

Domain of Function	Test Examples
Overall cognitive ability	Wechsler Adult Intelligence Scale-Revised (WAIS-R); Raven Progressive Matrices; syntactic reasoning
Attention and concentration	Digit-span test from WAIS-R; Bourdon-Wiersma Vigilance Test; Continuous Performance Test
Motor skills	Grooved pegboard; finger-tapping; Santa Ana dexterity test; simple reaction time
Visuomotor coordination	Digit-symbol from WAIS-R; Trails A and B; Aiming (Pursuit Aiming II)
Visuospatial relations	Block design from WAIS-R
Memory	Wechsler Memory Scale-Revised, including paired associates; Benton Visual Retention; serial digit learning
Affect and personality	Profile of Mood States (POMS); Minnesota Multiphasic Personality Inventory (MMPI); MMPI-2

SOURCE: Adapted from Fiedler et al., 1996; Proctor and White, 1990.

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G

CONSENSUS CONCLUSIONS ARRANGED BY HEALTH OUTCOME

Cancer

Sufficient Evidence of a Causal Relationship

- Benzene and acute leukemia

Sufficient Evidence of an Association

- Benzene and adult leukemia
- Solvents and acute leukemia

Limited/Suggestive Evidence of an Association:

- Tetrachloroethylene and dry-cleaning solvents and bladder cancer
- Solvents and bladder cancer
- Tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Organophosphorous insecticides and non-Hodgkin's lymphoma
- Carbamates and non-Hodgkin's lymphoma
- Benzene and non-Hodgkin's lymphoma
- Solvents and multiple myeloma
- Organophosphorous insecticides and adult leukemia
- Solvents and adult leukemia
- Solvents and myelodysplastic syndromes

Inadequate/Insufficient Evidence to Determine Whether an Association Exists:

- Solvents and oral, nasal, or laryngeal cancer
- Insecticides and pancreatic cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and esophageal cancer
- Solvents and stomach, rectal, or pancreatic cancer
- Solvents other than trichloroethylene and mixtures of benzene, toluene, and xylene and colon cancer
- Insecticides and solvents and hepatobiliary cancers
- Insecticides and lung cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and lung cancer

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- Solvents and bone cancer
- Solvents and melanoma or nonmelanoma skin cancer
- Insecticides and soft tissue sarcomas
- Lindane and solvents and breast cancer
- Solvents other than trichloroethylene and cervical cancer
- Solvents and ovarian or uterine cancer
- Insecticides and prostate, testicular, bladder, or kidney cancers
- Specific solvents other than tetrachloroethylene and dry-cleaning solvents and bladder cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Solvents and prostate cancer
- Insecticides and brain and other central nervous system cancers
- Specific solvents other than benzene and brain and other central nervous system cancers
- Specific solvents other than benzene and non-Hodgkin's lymphoma
- Insecticides and solvents and Hodgkin's disease
- Insecticides and specific solvents and multiple myeloma
- Specific solvents other than benzene and acute and adult leukemia
- Benzene and myelodysplastic syndrome
- Parental preconception exposure to insecticides and childhood leukemias, brain and other central nervous system cancers or non-Hodgkin's lymphoma
- Parental preconception exposure to solvents and neuroblastoma or childhood brain cancers

Limited/Suggestive Evidence of NO Association

- No findings

Neurologic Effects

Sufficient Evidence of a Causal Relationship

- No findings

Sufficient Evidence of an Association

- No findings

Limited/Suggestive Evidence of an Association:

- Organophosphorous insecticide exposure with OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)
- Solvents and neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

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Inadequate/Insufficient Evidence to Determine Whether an Association Exists:

- Insecticides and solvents and peripheral neuropathy
- Insecticides and solvents and Parkinson's Disease
- Insecticides and solvents and amyotrophic lateral sclerosis
- Insecticides and solvents and Alzheimer's Disease
- Solvents and multiple sclerosis
- Solvents and a long-term reduction in color discrimination
- Solvents and long-term hearing loss
- Solvents and long-term reduction in olfactory function

Limited/Suggestive Evidence of NO Association

- No findings

Reproductive Effects

Sufficient Evidence of a Causal Relationship

- No findings

Sufficient Evidence of an Association

- No findings

Limited/Suggestive Evidence of an Association:

- No findings

Inadequate/Insufficient Evidence to Determine Whether an Association Exists:

- Insecticides and solvents and male or female infertility after cessation of the exposure
- Parental preconception exposure to insecticides or solvents and spontaneous abortion or other adverse pregnancy outcomes
- Parental preconception exposure to insecticides or solvents and congenital malformations

Limited/Suggestive Evidence of NO Association

- No findings

Other Health Effects

Sufficient Evidence of a Causal Relationship

- Benzene and aplastic anemia

Sufficient Evidence of an Association

- Propylene glycol and allergic contact dermatitis

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Limited/Suggestive Evidence of an Association:

- Solvents and reactive airways dysfunction syndrome (RADS) which would be evident with exposure and could persist for months or years
- Solvents and hepatic steatosis
- Solvents and chronic glomerulonephritis
- Insecticides and allergic contact dermatitis

Inadequate/Insufficient to Determine Whether an Association Exists:

- Insecticides and aplastic anemia
- Solvents other than benzene and aplastic anemia
- Insecticides and solvents and irreversible cardiovascular outcomes
- Insecticides and solvents and persistent respiratory symptoms or impairment after cessation of exposure
- Solvents and alterations in liver function tests after cessation of exposure
- Solvents and cirrhosis
- Solvents and chronic pancreatitis or other persistent gastrointestinal outcomes
- Solvents and the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus

Limited/Suggestive Evidence of NO Association

- No finding

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