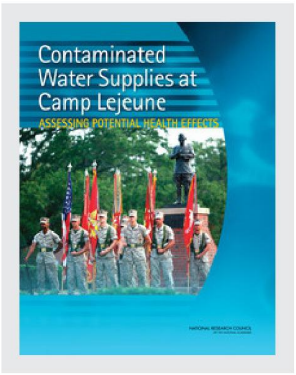
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SUGGESTED CITATION

National Research Council. 2009. *Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12618.

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Contaminated Water Supplies at Camp Lejeune

ASSESSING POTENTIAL HEALTH EFFECTS

Committee on Contaminated Drinking Water at Camp Lejeune

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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This project was supported by Contract W81K04-07-C-0005 between the National Academy of Sciences and the U.S. Department of the Navy. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-13699-0
International Standard Book Number-10: 0-309-13699-7

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Preface

Two water-supply systems on the Marine Corps Base Camp Lejeune in North Carolina were contaminated with the industrial solvents trichloroethylene (TCE) and perchloroethylene (PCE). The contamination appears to have begun in the middle 1950s and continued until the middle 1980s, when contaminated supply wells were shut down. The sources of the contamination were an off-base dry-cleaning establishment and on-base industrial activities. Contaminated water was distributed to enlisted-personnel family housing, barracks for unmarried personnel, base administrative offices, schools, a hospital, industrial areas, and recreational areas.

Many former residents and employees of the base have raised questions about whether health problems that they or members of their families have experienced could be related to their exposure to the contaminated water. A few studies have been performed on former residents of the bases, but they were focused only on selected birth and childhood health outcomes. As directed by Congress, the U.S. Navy requested a study by the National Research Council to review the scientific evidence on associations between historical data on prenatal, childhood, and adult exposures to contaminated water at Camp Lejeune and adverse health effects.

In response to the Navy's request, the National Research Council convened the Committee on Contaminated Drinking Water at Camp Lejeune, which prepared this report. The members of the committee were selected for their expertise in epidemiology, toxicology, exposure analysis, environmental health, groundwater modeling, biostatistics, and risk assessment (see Appendix A for biographic information on the members).

To help the committee in its review, meetings were held in September and November 2007 and September 2008 to gather information from scientists and those who chose to inform the committee regarding their experiences in relation to the water contamination at Camp Lejeune. The committee is grateful to the people who gave presentations on their investigations into the contamination of the water supplies at Camp Lejeune and on general issues related to groundwater modeling, including a series of responses to followup queries from members of the committee: Frank Bove and Morris Maslia, of the Agency for Toxic Substances and Disease Registry (ATSDR); Richard Clapp, of Boston University and a member of ATSDR's community-assistance panel; Marcia Crosse, of the U.S. Government Accountability Office; and Mary Hill, of the U.S. Geological Survey. The committee also thanks the many former residents of and workers at Camp Lejeune who contributed their time to attend the public meetings and share their experiences and concerns (see Appendix B). In particular, the committee acknowledges Jerry Ensminger and Jeff Byron, who served as representatives of people who were unable to attend the meetings. The committee is thankful for the useful input from Amy Kyle, of the University of California at Berkeley, in the early deliberations of this study. It would also like to acknowledge the advice that it received from Michael Luster, formerly with the National Institute for Occupational Safety and Health, who was a consultant to the committee on immunotoxicity issues.

The U.S. Marine Corps provided the committee with support throughout the study. Kelly Dreyer and Scott Williams helped to coordinate a meeting at Camp Lejeune and responded to the committee's requests for background information. The committee is grateful to the staff of the Installation and Environment Department at Camp Lejeune for providing a guided tour of the areas of the base where the sup-

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ply wells and water-treatment plants were and of the residential and work areas that were served by the contaminated water systems.

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's Report Review Committee. The purpose of the 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 of 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 thank the following for their review of this report: John L. Adgate, University of Minnesota; Mary P. Anderson, University of Wisconsin; Richard Clapp, Boston University; Mary C. Hill, U.S. Geological Survey; Margot Krauss, consultant; Lawrence H. Lash, Wayne State University; Rosalind A. Schoof, Integral Consulting, Inc.; Michael A. Stoto, Georgetown University; Clifford Weisel, University of Medicine and Dentistry of New Jersey; and Raymand S. Yang, Colorado State University.

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 the report was overseen by the review coordinator, George M. Rusch, Honeywell Inc., and the review monitor, George M. Hornberger, Vanderbilt University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the author committee and the institution.

The committee is grateful for the assistance of National Research Council staff in preparing the report. In particular, Susan Martel, who served as project director, skillfully coordinated the project and contributed to the committee's report, devoting patient, concerted effort to resolving the many controversies that evolved through the course of the project. Other staff members who contributed are James Reisa, director of the Board on Environmental Studies and Toxicology; Norman Grossblatt, senior editor; Mirsada Karalic-Loncarevic, manager of the Technical Information Center; Tamara Dawson, program associate; and Patrick Baur, research assistant.

The committee members devoted substantial effort to the development of this report through rounds of discussion, deliberation, writing, and rewriting. They came to their task with a wide variety of perspectives based on disciplinary training, research pertaining to the chemicals and health effects of concern, and ideology; but all shared a commitment to bring the best knowledge possible to bear on important health issues and to assist the sponsor and former Camp Lejeune residents by offering an assessment and a scientific perspective that can help to bring this long-standing and sometimes contentious concern closer to a resolution.

This report focuses on what scientific evidence can say about the causal relationship of past exposures and health outcomes. It is important to understand the difference between how scientific evidence is used in this context, compared to how it is used in the context of regulatory risk assessment and prevention. We should be clear that the evaluation we conducted was not for the purposes of regulatory risk assessment, and the prepublication version of this report may not have made this distinction clear enough to all readers. The following excerpt from the 2003 Institute of Medicine report, *Gulf War and Health Volume 2* provides a useful explanation of this important distinction.[2]

> *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 regu-*

[2]This paragraph was added after the release of the prepublication to clarify an issue that confused some readers of the prepublication.

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lation). 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.

David A. Savitz, *Chair*
Committee on Contaminated Drinking Water
at Camp Lejeune

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Abbreviations

ALL	acute lymphocytic leukemia
ALS	amyotrophic lateral sclerosis
ATSDR	Agency for Toxic Substances and Disease Registry
AWWA	American Water Works Association
BMI	body-mass index
BTEX	benzene, toluene, ethylbenzene, and xylene
CHAMPS	Naval Health Research Center's Career History Archival Medical and Personnel System
CI	confidence interval
CLW	Camp Lejeune water
CNS	central nervous system
CYP	cytochrome P-450
DCA	dichloroacetic acid
DCE	dichloroethylene
DCVC	*S*-(1,2-dichlorovinyl)-L-cysteine
DCVCS	DCVC sulfoxide
DCVG	*S*-(1,2-dichlorovinyl)glutathione
DCVT	*S*-(1,2-dichlorovinyl)thiol
DEP	Department of Environmental Protection
DNAPL	dense nonaqueous-phase liquid
DOD	U.S. Department of Defense
DP	dipeptidase
EEG	electroencephalograpic
EPA	U.S. Environmental Protection Agency
FMO3	flavin-containing monooxygenase 3
GAO	U.S. Government Accountability Office
GIS	geographic information system
GST	glutathione *S*-transferase
IARC	International Agency for Research on Cancer
IFN-γ	interferon gamma
IL-4	interleukin-4
ILO	International Labor Organization
IOM	Institute of Medicine
JEM	job-exposure matrix
LBW	low birth weight
LMP	last menstrual period
LOAEL	lowest-observed-adverse-effect level
MC	methylene chloride
MCAS	Marine Corps Air Station
MCL	maximum contaminant level

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MCLG	maximum contaminant level goal
MOR	mortality odds ratio
MS	multiple sclerosis
NCDNRCD	North Carolina Department of Natural Resources and Community Development
ND	not detected
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse-effect level
NR	not reported
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
OU	operable unit
PAH	polycyclic aromatic hydrocarbon
PCE	perchloroethylene
PDD	personal delivered dose
PPARα	peroxisome-proliferator-activated receptor alpha
PPT	parts per trillion
PSOpS	Pumping Schedule Optimization System
PVC	polyvinyl chloride
RDD	relative delivered dose
RI	remedial investigation
RR	relative risk
SES	socioeconomic status
SGA	small for gestational age
SIR	standardized incidence ratio
SLE	systemic lupus erythematosus
SMR	standardized mortality ratio
SRR	standardized rate ratio
SSFL	Santa Susana Field Laboratory
STROBE	strengthening the reporting of observational studies in epidemiology
SVOC	semivolatile organic compound
TAL	target analyte list
TCA	trichloroacetic acid
TCE	trichloroethylene
TCE-O-CYP	trichloroethylene-oxide-cytochrome P-450 complex
TCL	target compound list
TCOG	trichloroethanol glucuronide
TCOH	trichloroethanol
TCVC	*S*-(1,2,2-trichlorovinyl)-L-cysteine
TCVCS	*S*-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide
TCVG	*S*-(1,2,2-trichlorovinyl) glutathione
TLBW	term low birth weight
UST	underground storage tank
VA	Department of Veterans Affairs
VC	vinyl chloride
VHL	von Hippel-Landau
VLBW	very low birth weight
VOC	volatile organic compound

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Contaminated Water Supplies at Camp Lejeune

ASSESSING POTENTIAL HEALTH EFFECTS

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Public Summary and Context

In the early 1980s, two water-supply systems on the Marine Corps Base Camp Lejeune in North Carolina were found to be contaminated with the industrial solvents trichloroethylene (TCE) and perchloroethylene (PCE). The water systems were supplied by the Tarawa Terrace and Hadnot Point water-treatment plants, which served enlisted-family housing, barracks for unmarried service personnel, base administrative offices, schools, and recreational areas. The Hadnot Point water system also served the base hospital and an industrial area and supplied water to housing on the Holcomb Boulevard water system (full-time until 1972 and periodically thereafter).

This report examines what is known about the contamination of the water supplies at Camp Lejeune and whether the contamination can be linked to any adverse health outcomes in former residents and workers at the base. Because of the technical nature of the report, this public summary is being provided to explain the committee's approach and reasoning, so that people who are not scientists can understand what was done and why. It attempts to place the committee's analysis and findings into the context of a larger discussion about environmental health issues at Camp Lejeune in a way that will be helpful to people who have personal concerns about the situation at the base. It also provides perspective on why the committee was unable to answer some questions.

THE CHARGE TO THE COMMITTEE

The National Research Council (NRC) conducted this review in response to a request from the U.S. Navy, the department under which the Marine Corps operates. The Navy was mandated by the U.S. Congress (Public Law 109-364, Section 318) to request a review by the NRC to address the evidence on whether adverse health outcomes are associated with past contamination of the water supply at Camp Lejeune. The NRC developed specific instructions for the scope of the review ("the charge"). It then recruited and appointed a committee of scientists with diverse but pertinent backgrounds and perspectives to carry out the review.

The charge had several elements. One was to review the scientific evidence about the kinds of adverse health effects that could occur after exposure to TCE, PCE, and other contaminants. The second was to evaluate studies that were performed or that are under way on former residents of the base and to consider how useful it will be to conduct additional studies. The third element was to identify scientific considerations that could help the Navy set priorities on future activities. The responsibility of the committee was to address its charge in a dispassionate, expert, and unbiased way. Analyses and findings were neither subject to oversight nor influenced by the agenda of any of the entities with responsibilities for Camp Lejeune, former or current residents of Camp Lejeune, or any other entity.

THE CONCERNS OF FORMER RESIDENTS AND WORKERS

The committee held three public meetings over the course of its study, two in Washington, DC (September 24, 2007, and September 12, 2008) and one in Camp Lejeune, NC (November 15, 2007). Former residents and other concerned individuals presented oral and written testimonies about their experiences at Camp Lejeune at those meetings. The committee also sought comments from consultants

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working with community groups seeking answers to questions about the water contamination. Although these encounters were not exhaustive in identifying all issues of concern or all perspectives, they gave the committee a chance to hear firsthand from people who have concerns. The committee sincerely appreciates the time and effort that went into the presentations, testimonies, and materials that were provided.

On the basis of the public input, the committee understands that some people believe that the Marine Corps has not responded appropriately to the contamination since it was first discovered. Some believe that the military leadership has not been fully forthcoming in providing data and information about the contamination and about the people who lived in affected areas. Some have concerns about whether information was disclosed or released in timely and appropriate ways. Questions have also been raised about the pace at which investigations have been conducted and whether the investigations are the most appropriate ones. Many expressed an interest in an unbiased and credible review.

Many of the people who addressed the committee have suffered from serious diseases or have family members or friends who have suffered. The committee was moved by the testimonies it heard and understands that some may have been looking for the committee to make a judgment on their particular case. However, science does not allow the committee to determine the cause of a specific case of disease. This may be hard to understand. Why would scientific experts not be able to determine whether a child's birth defect or a parent's cancer diagnosis was due to a chemical exposure? Unfortunately, for diseases that can have multiple causes and that develop over a long period of time, it is generally impossible to establish definitively the cause in individual cases. It was beyond the scope of the committee's charge to try to determine whether any particular case of a disease or disorder is associated with exposure to the water supply at Camp Lejeune.

Some parties contend that the Marine Corps has not done what it should to compensate them or to provide medical care for the harm they believe was caused by their exposure to the contaminated water supplies. In 2007, the U.S. Government Accountability Office (GAO) reported that former residents and employees of Camp Lejeune had filed more than 750 claims against the federal government related to the contamination. GAO also reports that the federal government is awaiting the results of a study on childhood cancers and birth defects before adjudicating claims. It was beyond the scope of the committee's charge to judge whether the military authorities acted appropriately from a legal or ethical perspective or fulfilled their responsibilities to those under their charge. It was also beyond the scope of the committee's charge to determine whether or how the military authorities should address claims made.

THE COMMITTEE'S REVIEW AND FINDINGS

The committee divided its review into two major categories: (1) evaluating the exposures of former residents and workers to the contamination of the Tarawa Terrace and Hadnot Point water-supply systems, and (2) evaluating the potential health effects associated with the water contaminants. The assessments were then considered together to ascertain whether conclusions could be drawn about whether any adverse health outcomes could be attributed to the water contaminants.

Exposures to Former Residents and Workers

The term "exposure" refers to contact with contaminants in air, water, or food that may occur through inhalation, ingestion, or dermal absorption (through the skin). In this case, it refers to drinking water that contains contaminants or using it for other purposes. Bathing and showering are relevant, as well as drinking, because TCE and PCE (and other solvents) can evaporate into the air (volatilize) when present in hot water used for bathing, showering, or washing dishes or clothing and can then be inhaled. All of these routes of exposure affect how the body metabolizes TCE and PCE, how the metabolites are distributed and cleared by the body, and how organ systems respond.

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It is also important to understand the duration of exposure, which is the length of time a person is exposed. An understanding of individual behaviors helps to estimate the degree of exposure that occurred. Water-related behaviors include water-consumption and showering or bathing patterns, but whether such information can be accurately recalled is questionable. The contaminated water systems also supplied nonresidential areas of the base, including schools, workplaces, recreational areas, and a hospital. Water-use patterns and behaviors in these settings are expected to vary substantially from those in residential areas. In addition, residential and nonresidential exposures could overlap, thus, exposing dividuals to contaminated water at multiple locations.

The Water Systems at Camp Lejuene

Figure 1 provides a simplified illustration of a water-supply system at Camp Lejeune. Water-supply wells collected groundwater and pumped it to a water-treatment plant when the wells were turned on. The wells were "cycled," meaning that only a few wells pumped water to the treatment plant at any given time. A few wells that supplied water to the Tarawa Terrace and Hadnot Point systems were contaminated by solvents from sources on and off the base. When the contaminated wells were in service, contaminated water was delivered to the water-treatment plant where water from several wells was mixed and processed before being distributed in the pipes that supplied water to the base. Thus, the contamination of the water supplies varied and was dependent on many factors, such as the time of operation of the contaminated wells, the water treatments used, and the rate at which water was supplied to the base.

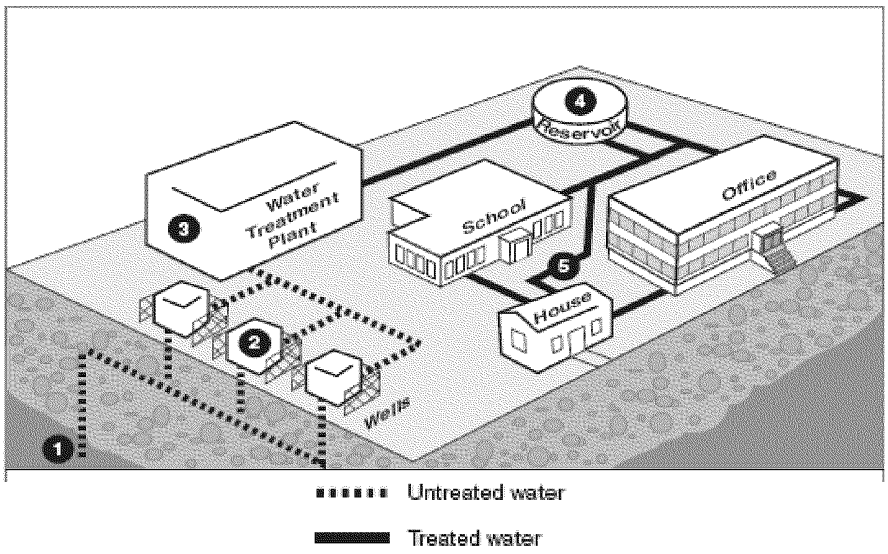


FIGURE 1 Conceptual model of a Camp Lejeune water system. (1) The drinking water at Camp Lejeune is obtained from groundwater pumped from a freshwater aquifer located approximately 180 feet below the ground. (2) Groundwater is pumped through wells located near the water-treatment plant. (3) In the water-treatment plant, the untreated water is mixed and treated through several processes: removal of minerals to soften the water, filtration through layers of sand and carbon to remove particles, chlorination to protect against microbial contamination, and fluoride addition to help to prevent tooth decay. (4) After the water is treated, it is stored in ground and elevated storage reservoirs. (5) When needed, treated water is pumped from the reservoirs and tanks to facilities such as offices, schools, or houses on the base. Source: GAO. 2007. Defense Health Care: Activities Related to Past Drinking Water Contamination at Marine Corps Base Camp Lejeune. GAO-07-276. Washington, DC: U.S. Government Accountability Office.

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Exposure Review

The committee's exposure evaluation involved identifying the contaminants of concern, their sources, and the concentrations estimated to be present in the water supplies over time. For Tarawa Terrace, the committee relied on work by the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR compiled the available information on the Tarawa Terrace water system and used computer models to simulate how contaminants moved underground, entered water-supply wells, and were distributed in the water supply. Contaminant measurements were only available from 1980 to 1985, so models were needed to make estimates of the concentrations of contaminants in the water supply in the preceding decades.

A similar historical reconstruction has not yet been performed for the Hadnot Point water system. To identify contaminants of concern there, the committee reviewed information on historical activities on the base (for example, building and chemical uses and sites of hazardous-waste storage or disposal) and findings from site investigations and plans for remedial action at waste sites. The committee also reviewed data available from testing records and other documents to get a preliminary characterization of the exposures that occurred. For some of its analyses, the committee focused on samples taken from "mixed water," that is, water mixed from several supply wells at the treatment plant, because those measurements were probably the most representative of the contaminant concentrations that were delivered to the taps on base. As was the case with Tarawa Terrace, contaminant measurements of the Hadnot Point system were only available from 1980 to 1985.

The major contaminants of the Tarawa Terrace and Hadnot Point systems are of a particular form that tends to serve as a continuing source of contamination even after the contaminants are underground. These are called "DNAPLs," which stands for dense nonaqueous phase liquids. DNAPLs are dense, so they have the potential to sink into the deeper aquifers. Such chemicals get trapped in the soil and dissolve slowly into groundwater. The geology of the area makes it probable that DNAPLs that were spilled on the ground or that were leaked or disposed of in the soil got into the groundwater that supplied some of the wells of the two systems.

The dry-cleaning solvent PCE is the primary contaminant of the Tarawa Terrace water-supply system. Spills and improper disposal of PCE by an off-base dry-cleaner contaminated the groundwater collected by on-base supply wells. Other contaminants detected in water-supply wells were TCE, 1,1-dichloroethylene (DCE), *cis*-1,2-DCE, *trans*-1,2-DCE, benzene, toluene, and vinyl chloride. Several of the contaminants (TCE, *cis*-1,2-DCE, *trans*-1,2-DCE, and vinyl chloride) may be the result of degradation of PCE in the soil and groundwater. There was some on-base contamination of the Tarawa Terrace supply system as well.

Sophisticated computer modeling techniques were used by ATSDR to make predictions about the monthly concentrations of PCE to which residents of Tarawa Terrace were exposed. To provide perspective on its estimates, ATSDR compared its monthly estimates with the U.S. Environmental Protection Agency (EPA) maximum contaminant level (MCL) for PCE in drinking water of 5 µg/L, which was established in 1985. The model estimated that starting in November 1957, the concentration of PCE delivered to residents exceeded that MCL and remained well above it until the wells were closed in 1985.

Some of the modeling approaches used by ATSDR were "cutting-edge," meaning that they used computer codes and modeling techniques that are still in the research stage and have yet to be validated. Furthermore, the absence of measurement data for the first 30 years of the contamination period means the predictions, even if based on validated codes and models, cannot be evaluated for accuracy. The actual concentrations may have been higher or lower than the predictions, but that cannot be assessed. Other uncertainties were introduced into the models because assumptions had to be made about how the water system was operating. For example, little information was available on which wells were supplying water at specific time periods, so assumptions had to be made about when the contaminated wells were operating. Another uncertainty is that the models did not take into account the DNAPL form of pollutants. Given the multiple uncertainties and likely variation in contaminant concentrations, the committee con-

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cluded that the Tarawa Terrace modeling predictions should only be used to provide a general estimate of the timeframe and magnitude of exposure.

The contamination of the Hadnot Point system was more complex than Tarawa Terrace. There were multiple sources of pollutants, including an industrial area, a drum dump, a transformer storage lot, an industrial fly ash dump, an open storage pit, a former fire training area, a site of a former on-base dry cleaner, a liquids disposal area, a former burn dump, a fuel-tank sludge area, and the site of the original base dump. The available data on contaminant measurements taken in the 1980s show that TCE and *trans*-1,2-DCE were the contaminants found most often in mixed-water samples, with a few detections of PCE, methylene chloride, and vinyl chloride. The nature of the hazardous-waste sites in the vicinity of the Hadnot Point supply wells suggests that other contaminants may have been present. For example, tests of samples taken from special monitoring wells installed after the contamination was discovered have detected fuel constituents and metals, compounds that were not routinely analyzed in the water samples taken in the 1980s.

Recommendations

- For the purposes of epidemiologic studies, the results of the Tarawa Terrace historical reconstruction can be used to characterize people as being exposed or unexposed on the basis of date and location of residence or workplace. The monthly estimates imply more accuracy than is appropriate and should not be used to characterize exposure of individual people.
- Because any groundwater modeling of the Hadnot Point system will be fraught with considerable difficulties and uncertainties, simpler modeling approaches should be used to assess exposures from the Hadnot Point water system. Simpler modeling will not reduce the uncertainty associated with the estimates, but they have the advantage of providing a broad picture of the timeframe and magnitude of exposure encountered by people who used water from that system more quickly and with less resources than complex modeling exercises.
- To facilitate better understanding of the contamination on the base, the Marine Corps should develop a comprehensive and accessible database of water-quality measurements taken from the base.

Potential Health Effects

The committee undertook four kinds of reviews to determine what kinds of diseases or disorders (adverse health effects) have been found to result from exposure to TCE and PCE: (1) review of epidemiologic studies of solvents and their effects, including studies in occupational and industrial settings and community studies; (2) review of epidemiologic studies of other communities with solvent-contaminated water supplies; (3) review of toxicologicstudies conducted in animals and humans to test for health effects of TCE and PCE; and (4) review of studies conducted specifically on the Camp Lejeune population.

Review of Epidemiologic Evidence on Solvents

Epidemiologic studies examine whether people with greater exposure to particular chemicals have greater frequency of disease than people with lesser or no exposure (also referred to as greater incidence or greater risk of disease). To manage the review of the vast amount of peer-reviewed scientific literature on TCE and PCE, the committee began with a comprehensive review of the epidemiologic studies of those solvents that was conducted by the Institute of Medicine (IOM) in 2003. IOM categorized the evidence according to an established scheme accepted by the Department of Veteran's Affairs in evaluating risks to veterans of the Vietnam War and the Gulf War. These categories are shown in Box 1. The

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Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects

BOX 1 Five Categories Used by IOM to Classify Associations

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 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 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 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 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.

Source: IOM (Institute of Medicine). 2003. Gulf War and Health, Vol. 2, Insecticides and Solvents. Washington, DC: National Academies Press.

committee identified new studies published from 2003 to 2008 and considered whether they changed the conclusions in the IOM report. The studies included people exposed in occupational situations and in community settings.

IOM's approach to evaluating the literature is to determine whether a "statistical association" exists between the chemicals and diseases and disorders. When studies are conducted properly, a statistical association means that people who are exposed to the chemicals are more likely to have or develop the disease or disorder than people who are not exposed. A statistical association, however, does not establish

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that the chemicals cause the diseases or disorders. Judgment about the quality of each study and additional supporting evidence from other studies are needed. Statistical associations are often represented by numeric estimates, known as "relative risks" or "odds ratios." The estimates describe the relative frequency of disease in groups with higher exposures compared with groups with lower or no exposure. For example, in a study in which individuals are classified as either exposed or unexposed, a relative risk of 2 means that exposed people in the study were twice as likely to develop the disease as people who were not exposed.

As shown in Box 2, all the health outcomes reviewed were placed into one of two categories. The strongest evidence was in the category of *limited/suggestive of an association*, which means that there is some evidence that people who were exposed to TCE or PCE were more likely to have the disease or disorder but that the studies were either few in number or had important limitations. In many cases, the studies could not separate out the effects of individual chemicals because the people were exposed to mixtures. Some of these studies were of highly exposed groups of workers where detection of effects would be expected if present. Such studies might reach conclusions about solvents in general but not about TCE or PCE specifically. For diseases and disorders where the evidence is limited/suggestive of an association, the committee has concluded that the epidemiologic studies give some reason to be concerned that sufficiently high levels of the chemical may cause the disease, but the studies do not provide strong evidence that they actually do so.

The majority of the health outcomes reviewed by the committee were placed into the category of *inadequate/insufficient evidence to determine whether an association exists*, which means that the studies were too few in number, limited in quality, inconsistent, or inconclusive in results to make an informed assessment. It also means that such an association cannot be ruled out. For diseases and disorders in this category, the committee has concluded that the epidemiologic studies cannot tell us whether exposure to the chemicals is associated with the disease or not.

The committee is aware that some health outcomes reported by former residents of the base (for example, male breast cancer and second-generation effects) are not cited in Box 2. The absence of inclusion of specific health outcomes does not mean that such effects are unrelated to exposures from the contaminated water supplies at Camp Lejeune. Rather, those outcomes have not been specifically investigated or, if they were considered, the studies were too small or of insufficient quality to allow conclusions to be drawn.

Review of Epidemiologic Evidence from Community Studies

The committee decided to consider the subset of epidemiologic studies that were conducted in communities exposed to solvents in their water supplies in more detail. Because these studies involved populations and exposure situations that more closely resemble those at Camp Lejeune, some relevant implications might be learned. A few studies reported certain diseases and disorders, such as congenital heart defects, spontaneous abortions, and very low birth weight. However, the studies reported differing effects, so generally they did not confirm each other. In general, the studies had limitations in their design that are unavoidable because of the circumstances that gave rise to them. The limitations include lack of data on levels of contaminants in the water, lack of adequate information about diseases and disorders in the population, and relatively small populations. These factors limit the capacity of such studies to detect associations even if they exist. Limitations in such studies often mean that people in the study communities can only be classified into two groups to reflect exposure to contamination—those exposed and those considered unexposed. Such classification is a crude way to address exposure because it can make it more difficult to detect any effects that might occur. Another common limitation of community studies in general is that they are not able to account for other factors that may affect the likelihood of disease. Furthermore, the studies face the difficult task of addressing diseases that are relatively uncommon. It is harder to find enough cases of uncommon diseases to make comparisons when studying relatively small

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BOX 2 Categorization of Health Outcomes[a] Reviewed in Relation to TCE, PCE, or Solvent Mixtures

Sufficient Evidence of a Causal Relationship

- No outcomes

Sufficient Evidence of an Association

- No outcomes

Limited/Suggestive Evidence of an Association

- Esophageal cancer (PCE)
- Lung cancer (PCE)
- Breast cancer (PCE)
- Bladder cancer (PCE)
- Kidney cancer
- Adult leukemia (solvent mixtures)
- Multiple myeloma (solvent mixtures)
- Myleodysplasic syndromes (solvent mixtures)
- Renal toxicity (solvent mixtures)
- Hepatic steatosis (solvent mixtures)
- Female infertility (with concurrent exposure to solvent mixtures)
- Miscarriage (with exposure to PCE during pregnancy)
- Scleroderma (solvent mixtures)
- Neurobehavioral effects (solvent mixtures)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Oral/pharyngeal cancer
- Nasal cancer
- Laryngeal cancer
- Esophageal cancer (TCE)
- Stomach cancer
- Colon cancer
- Rectal cancer
- Pancreatic cancer
- Hepatobiliary cancer
- Lung cancer (TCE)
- Bone cancer
- Soft tissue sarcoma
- Melanoma
- Non-melanoma skin cancer
- Breast cancer (TCE)
- Cervical cancer
- Ovarian/uterine cancer
- Prostate cancer
- Bladder cancer (TCE)
- Cancer of the brain or central nervous system
- Non-Hodgkin lymphoma
- Hodgkin disease
- Multiple myeloma
- Adult leukemia
- Myelodysplasic syndromes
- Childhood leukemia
- Childhood neuroblastoma
- Childhood brain cancer
- Aplastic anemia
- Congenital malformations
- Male infertility
- Female infertility (after exposure cessation)
- Miscarriage, preterm birth, or fetal growth restriction (from maternal preconception exposure or paternal exposure)
- Preterm birth or fetal growth restriction (from exposure during pregnancy)
- Cardiovascular effects
- Liver function or risk of cirrhosis
- Gastrointestinal effects
- Renal toxicity
- Amyotrophic lateral sclerosis
- Parkinson disease
- Multiple sclerosis
- Alzheimer disease
- Long-term reduction in color discrimination
- Long-term hearing loss
- Long-term reduction in olfactory function

Limited/Suggestive Evidence of No Association

- No outcomes

[a]Outcomes for TCE and PCE unless otherwise specified.

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populations. The committee concluded that the evidence provided by this subset of epidemiologic studies needs further support and confirmation before they can be considered significant on their own.

Review of the Toxicologic Evidence

Toxicologic studies are mainly laboratory experiments, usually conducted on animals. The committee's review on TCE and PCE were in part based on previously published toxicologic reviews but were mainly based on analyses of recently published studies. The studies were analyzed using criteria for good study design and degree of agreement between the conclusions and the data presented. Further, the committee took into consideration the quality and reliability of studies, consistency of findings of similar studies, understanding of the biologic processes, toxicologic significance, dose- and duration-dependence, and understanding of whether effects observed in animals are predictive of human risks. Each chemical was reviewed for effects on the major organ systems—for example, liver, kidneys, lungs, reproductive system, nervous system, and immune system.

In animal experiments, TCE was reported to cause kidney and testicular cancers in rats and liver and lung cancers in mice. PCE was reported to cause liver cancer in mice and mononuclear cell leukemia and kidney cancer in rats. Differences in how these chemicals are handled in the body by rodents and humans, as well as current scientific understanding of how these tumors develop, led the committee to the conclusion that kidney cancer is the most relevant to humans.

For other kinds of adverse health effects, kidney toxicity and liver toxicity were observed in rodents given high doses of TCE and PCE. Effects on male rodent fertility, but not female fertility, were observed. Neither chemical caused birth defects in rats. There were some adverse effects on offspring of pregnant female rats exposed to PCE but to not TCE. Adverse changes in some nervous system measurements were seen in some TCE and PCE studies. TCE causes some effects on the immune system of sensitive strains of mice, but there are few immunotoxicity studies on PCE.

When possible, the committee identified the lowest dose of TCE or PCE at which adverse effects were observed in animal studies (the dose is called the lowest-observed-adverse-effect level or LOAEL). To put these doses in perspective, the committee did a comparison of the doses with approximated doses to former residents that were estimated from concentrations of TCE and PCE measured in mixed water.[1] Because of the known variation in contaminant concentrations, the range used for the comparison included the highest measured concentrations of TCE and PCE in mixed water, one-half those concentrations, and twice the highest measured concentrations. The adverse health effects considered for this comparison were those thought to be most relevant to humans (kidney cancer, renal toxicity, and immunosuppression for TCE, and renal toxicity and neurotoxicity for PCE). This comparison is not an assessment or prediction of risk and can only give a general indication of the degree of difference between doses that caused a response in laboratory animals and doses to former residents of Camp Lejeune. The comparison reflects estimated combined daily doses from all three routes of exposure (ingestion, inhalation, and skin contact) that could have occurred for adults and children at Camp Lejeune. Results of the comparison suggest that the highest levels of either TCE or PCE measured in the mixed-water samples at Camp Lejeune were much lower than the lowest dose that caused adverse effects in the most sensitive strains and species of laboratory animals. The lower levels of exposure may be of some concern for effects on neurotoxicity and immunotoxicity, but further research is needed to evaluate the specific effects of TCE and PCE and whether they are relevant to humans.

Consideration of the Epidemiologic and Toxicologic Evidence Together

The committee considered collectively what is known about adverse health effects that are asso-

[1]A dissenting viewpoint on the conduct of this comparison is provided in Chapter 4.

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ciated with exposure to TCE and PCE from human epidemiologic and animal toxicologic studies. Evidence on similar outcomes reported in animal and human studies were compared to see whether the data were supportive of the potential health consequences of exposure to TCE and PCE in the water supply.

Review of epidemiologic studies on cancer outcomes provided limited/suggestive evidence for an association between chronic exposure to TCE or PCE and kidney cancer and to PCE and cancers of the esophagus, lungs, breast, and bladder. For these outcomes, the toxicologic evidence was strongest for kidney cancer.

Noncancer effects that were found to be similar in humans and laboratory animals included adverse effects on the liver, kidneys, and nervous and immune systems. In the epidemiologic literature, toxic effects on the liver and kidneys appeared to be related to short-term inhalation of high concentrations of solvents as opposed to longer-term exposure at lower concentrations. Support for these effects observed in toxicologic studies come from rodents exposed to high concentrations of TCE and PCE. For kidney effects, adverse findings were only found in male rats. Epidemiologic studies of occupational exposure to mixed solvents showed limited/suggestive evidence of neurobehavioral effects, and toxicologic studies of TCE showed some decrements in neurobehavioral outcomes. For effects on the immune system, epidemiologic studies showed limited/suggestive evidence for an association with mixed solvent exposure for certain immunologically mediated diseases. Toxicologic studies also showed that TCE can affect the immune system, as shown by immunosuppression and worsening of preexisting autoimmune diseases. These findings are shown in Table 1. The absence of other diseases and disorders in the table does not mean that such outcomes are irrelevant or unworthy of study, but that the findings for them were inconsistent between the toxicologic and the epidemiologic evidence or were not addressed in the available studies.

Review of Camp Lejeune Studies

Only a few studies have been conducted on the Camp Lejeune population, and these have focused on health effects in people who were exposed as children or while their mothers were pregnant with them. One study evaluated pregnancy outcomes among women who lived in base housing from 1968 to 1985.

Although the water contamination probably began before 1968, ATSDR selected 1968 as its starting point because electronic birth certificates became available that year. ATSDR compared data on premature births, births of babies who were small relative to other babies from pregnancies of similar duration (small for gestational age), and birth weights between mothers who were exposed and those who were unexposed. Whether mothers were exposed was determined by where they lived on the base when the child was born, not taking into account whether they moved during the pregnancy. Two analyses were performed; one that evaluated residents of Hadnot Point and Tarawa Terrace and one that focused only on Tarawa Terrace residents.

In both analyses, no clear associations were found between mean birth weight, preterm birth, or small for gestational age. However, a comparison of subgroups within the Tarawa Terrace population found a weak association between PCE exposure and small-for-gestational-age births for children of women over 35 or of women who had prior miscarriages. However, a limitation of this conclusion is that the decision to perform this analysis was added after the original design of the study. It was not one of the hypotheses or theories set out before the study. Therefore, scientists give this finding less weight.

The findings from these analyses are no longer valid. After the study was completed, ATSDR discovered that that a residential area it classified as unexposed (Holcomb Boulevard) received water from the Hadnot Point system for the first 4 years of the study period, and the study results must be reanalyzed to correct for this mistake in classification. ATSDR has indicated that it will reanalyze the results of the study using exposure estimates from its groundwater modeling of the Tarawa Terrace and Hadnot Point systems.

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TABLE 1 Similar Health Effects Found in Epidemiologic and Toxicologic Studies

Effects	Epidemiologic Evidence	Toxicologic Evidence
Kidney cancer	Limited/suggestive for TCE and PCE	TCE and PCE (limited to male rats)
Liver toxicity	Limited/suggestive for solvents and hepatic steatosis[a]	TCE and PCE (liver damage)
Kidney toxicity	Limited/suggestive for solvents	TCE and PCE (limited to male rats)
Neurobehavioral effects	Limited/suggestive for solvents (effects on visuomotor and motor function, fatigue, headache, deficits in concentration)	TCE: central nervous system depression, attention deficits, deficits in visual discrimination, altered visual evoked potentials[b] PCE: anesthetic effects; changes in behavior and neurochemical markers
Immunologic effects	Limited/suggestive for solvents and glomerulonephritis[c] and scleroderma[d]	TCE: sensitization, immunosuppression, influence autoimmune disease (in sensitive strains of mice)

[a]Hepatic steatosis is fatty accumulation in the liver.
[b]Electrical response recorded by a skull electrode after a visual stimulus (e.g., a flash).
[c]Glomerulonephritis is a disease that affects kidney function.
[d]Scleroderma is a disease resulting in abnormal growth of connective tissue.

ATSDR also has a study under way on prenatal exposure to water-supply contaminants and birth defects and childhood cancer. The specific outcomes being studied are childhood leukemia, childhood non-Hodgkin lymphoma, spina bifida, anencephaly, cleft lip, and cleft palate. These outcomes are rare, and given the number of study participants, it appears that the statistical power of this study could limit its ability to detect associations. The study is also awaiting the completion of groundwater modeling of the Hadnot Point water system so that differences in exposure can be assessed.

Recommendations

- The committee recommends that ATSDR go forward with reanalyzing its study of birth outcomes to correct for errors in exposure classification without awaiting the results of groundwater modeling of the Hadnot Point system. For the reasons given earlier, such modeling is unlikely to yield reliable quantitative estimates of exposure that would refine exposure classification for epidemiologic study.
- Despite the committee's concerns about the statistical power of the study of birth defects and childhood cancer, it recommends that the study be completed as soon as possible. Simpler approaches to groundwater modeling should be performed to support the exposure classification in the study rather than performing the same type of complex groundwater modeling that was performed for Tarawa Terrace.

The Feasibility and Utility of Future Studies of the Camp Lejeune Population

ATSDR has evaluated the feasibility of conducting three additional studies of the Camp Lejeune population, including a health survey and studies that would evaluate deaths from all causes and cancer incidence among former residents and workers. ATSDR identified some of the same diseases and disorders identified in the committee's review as being of interest. These included kidney cancer, lung cancer, breast cancer, scleroderma, liver disease, kidney disease, and spontaneous abortion. ATSDR also identified additional outcomes of possible interest for its study.

Difficulties with performing the studies are identifying, locating, and recruiting the study participants and obtaining reliable health information on them in an efficient manner. The committee found that

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although ATSDR did consider the major issues bearing on the feasibility of the proposed studies and proposed reasonable approaches to conducting the studies, there remain serious, unresolved questions about the feasibility and ultimate value of the studies. For example, it is not clear that the cancer incidence study could be performed successfully, because it is contingent on the cooperation of many state cancer registries. Even with cooperation, the statistical power to compare groups of interest across the range of outcomes has yet to be assessed. Statistical power is also an issue with the mortality study.

The committee also reviewed ATSDR's plans for a health survey that was generated in response to a congressional directive. The survey would seek information on residential history and various health outcomes. Although the survey could contribute to designing future studies at Camp Lejeune, its success depends on getting adequate participation (at least 60%). Even if satisfactory participation is achieved, there are concerns that there could be bias in the reported data because people who have experienced disease or illness are more likely to participate in the survey.

After reviewing the study plans and feasibility assessments, the committee concluded that most questions about whether exposures at Camp Lejeune resulted in adverse health effects cannot be answered definitively with further scientific study. There are two main reasons for this. First, it is not possible to reliably estimate the historical exposures experienced by people at the base. Second, it will be difficult to detect any increases in the rate of diseases or disorders in the study population. Most of the health effects of concern are relatively rare, which means that very large numbers of people are needed to detect increased cases. Although the total number of people who have lived at Camp Lejeune while the Tarawa Terrace and Hadnot Point water supplies were contaminated is sizable, the population is still unlikely to be large enough to detect effects, other than common diseases or disorders, of concern. Another factor is that the population was relatively young, so many who would be studied are in an age range in which chronic diseases are rare. Yet another factor is that the people tended to live on the base for a relatively short time, resulting in a small increase in risk of disease at most, making it difficult to rule out other exposures or factors that could have contributed to disease or illness. All these factors make it unlikely that the proposed studies, even if the notable uncertainties about feasibility are resolved favorably, will produce results of sufficient certainty to resolve the question of whether Camp Lejeune residents suffered adverse health effects from exposure to contaminated water.

The available scientific information does not provide a sufficient basis for determining whether the population at Camp Lejeune has, in fact, suffered adverse health effects as a result of exposure to contaminants in the water supplies. On the one hand, several lines of scientific reasoning suggest such effects are unlikely to have occurred. The evidence includes a substantial body of research on the toxicology of TCE and PCE that indicate that the exposures required to cause adverse effects in laboratory animals were much larger than the highest measurements available on the Camp Lejeune water supplies; evidence that humans have lower sensitivity to TCE and PCE than rodents; epidemiologic data largely from occupational settings with higher, longer-term exposures to TCE and PCE that has not generated compelling evidence of adverse health effects; and the relatively short-term, intermittent nature of the exposures incurred at Camp Lejeune. On the other hand, the possibility that health effects have been produced by the contaminant exposures at Camp Lejeune cannot be ruled out. Some effects of TCE or PCE exposure might have occurred below the level of detection in toxicologic studies, which focused on single contaminant exposures at high doses, used genetically homogeneous animal strains, and necessarily involved extrapolation across species. In addition, the population exposed at Camp Lejeune is more diverse and possibly more susceptible than those who have been exposed to TCE and PCE in occupational settings, and the actual concentrations of PCE and TCE and the presence of additional water contaminants are poorly documented and could thus be higher or more complex than the limited historical measurements suggest. There were divergent views among the committee members about the probability that each would assign to whether adverse health effects have in fact occurred, but there was consensus among them that scientific research is unable to provide more definitive answers to that question.

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Conclusion and Recommendation

- It cannot be determined reliably whether diseases and disorders experienced by former residents and workers at Camp Lejeune are associated with their exposure to contaminants in the water supply because of data shortcomings and methodological limitations, and these limitations cannot be overcome with additional study. Thus, the committee concludes that there is no scientific justification for the Navy and Marine Corps to wait for the results of additional health studies before making decisions about how to follow up on the evident solvent exposures on the base and their possible health consequences. The services should undertake the assessments they deem appropriate to determine how to respond in light of the available information.

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Summary

In the early 1980s, two water-supply systems on the Marine Corps Base Camp Lejeune in North Carolina were found to be contaminated with the industrial solvents trichloroethylene (TCE) and perchloroethylene (PCE). The water systems were supplied by the Tarawa Terrace and Hadnot Point water-treatment plants, which served enlisted-family housing, barracks for unmarried service personnel, base administrative offices, schools, and recreational areas. The Hadnot Point water system also served the base hospital and an industrial area and supplied water to housing on the Holcomb Boulevard water system (full-time until 1972 and periodically thereafter).

PCE was the primary contaminant found in the wells serving the Tarawa Terrace system. The chemical was used by an off-base dry cleaner (ABC One-Hour Cleaners), and the groundwater became contaminated with PCE as a result of spills and improper disposal practices. Contamination of the wells from that source is estimated to have begun as early as 1953, the year when dry-cleaning operations began. There were also other on-base sources of contamination in the Tarawa Terrace system that had a smaller impact on the water supply. The contamination of the Hadnot Point water supply was more complex and involved multiple sources and multiple contaminants. The primary contaminant found in those wells since monitoring began in the 1980s was TCE. It is likely that multiple sources contributed to the TCE contamination, including on-base spills at industrial sites and leaks from underground storage tanks and drums at dumps and storage lots. The Hadnot Point water-treatment plant began operating in 1943, but no estimates have yet been made of when the contamination began. Wells in both systems that were contaminated in the early 1980s were closed in the period November 1984–May 1985, and the entire Tarawa Terrace water-treatment plant was closed in 1987.

There has been considerable public controversy over the potential health consequences for former residents who were exposed to the contaminated water. TCE and PCE are known to have toxic effects in animals and in humans, so it is important to understand the scale and extent of exposure that occurred at the base to assess effects on the health of former residents. Only a few studies have been performed specifically on former residents of the base. To supplement those evaluations and to help to inform decisions about addressing health claims, the U.S. Navy was directed by Congress (Public Law 109-364, Section 318) to ask the National Research Council to address independently questions about whether any health outcomes are associated with past contamination of the water supply at Camp Lejeune. The National Research Council assembled a multidisciplinary committee of environmental scientists, toxicologists, epidemiologists, and biostatisticians to review the scientific evidence on associations between adverse health effects and historical data on prenatal, childhood, and adult exposures to contaminated drinking water at Camp Lejeune. The committee was asked to focus its attention on toxicologic and epidemiologic literature on TCE and PCE and to consider studies of Camp Lejeune residents and other populations exposed to the contaminants of concern and proposals for additional studies of Camp Lejeune residents.

To address its task, the committee divided its investigation into two major categories: assessing exposure to contaminants in the water supply and assessing the possible health effects associated with the contaminants. The reviews were then integrated to ascertain whether conclusions could be drawn about the likelihood that outcomes in people who lived or worked in the affected areas of the base were caused by the contaminated water supplies. The contribution of past and current studies of the Camp Lejeune population was evaluated, as was the potential contributions of future research on this population.

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EXPOSURE-ASSESSMENT EVALUATION

To understand the exposures that occurred because of the contamination of water supplies at Camp Lejeune, it is important to characterize the contamination—including its location, magnitude, duration, and variability—and the individual water-use patterns and other water-related behavior of the population that was exposed. The first component involves identifying the contaminants of concern, their sources, and their estimated concentrations in any particular water-supply system over time. The second component is to characterize how members of the population may have been exposed to the contaminated water supply at home, at work, and in other settings through water consumption, dermal contact, and inhalation of volatile compounds during showering, bathing, dishwashing, and other activities. Such factors are important determinants of exposure and are likely to vary widely in the population.

Water-Supply Contamination

The Tarawa Terrace and Hadnot Point water-supply systems began operating in 1952 and 1943, respectively. From a conceptual standpoint, their operations were similar. Water-supply wells collected groundwater and pumped it to a water-treatment plant. The wells were "cycled," meaning that only a subset of wells pumped water to the treatment plant at any given time. A few wells on both systems were contaminated. When those wells were operating, they delivered contaminated water to the treatment plant, where it was mixed with water from other wells and processed before being distributed on the base. Over the years, wells were added and some were taken temporarily offline or were closed for various reasons. Thus, concentrations of contaminants to which people were exposed varied substantially on a short-term and long-term basis.

The residential areas served by the two water systems were primarily enlisted family housing and barracks for unmarried service personnel. Thus, many of the exposed were young families and people of reproductive age. The population was also transient, with some people living on the base for a few months for training or for a few years for longer assignments.

Tarawa Terrace

The committee reviewed the available data on the exposures that occurred at Camp Lejeune. For Tarawa Terrace, the Agency for Toxic Substances and Disease Registry (ATSDR) performed a historical reconstruction of contamination scenarios and used its model to estimate the concentrations of chemical contaminants that occurred during different periods. ATSDR's historical reconstruction involved investigation into operations of the off-base dry cleaner, on-base operations, operation of water-supply wells and water-treatment plants, water-monitoring data, groundwater flow, and other data relevant to providing a chronology of events related to the contamination. The primary contaminant identified as present at Tarawa Terrace is PCE. PCE is typically degraded by natural processes in the soil and groundwater to TCE, *trans*-1,2-dichloroethylene (1,2-DCE), and vinyl chloride. Groundwater models were used to reconstruct the migration of PCE from the dry cleaners to the water-supply wells serving Tarawa Terrace, and then mixing models were used to predict monthly concentrations of PCE and its degradation products in finished water (groundwater that was treated at a water-treatment plant for delivery to residences) from 1957 to 1985. Because the models were based on several simplifying assumptions and were calibrated by using a small number of water-quality measurements taken during a narrow window (1980-1985) of the total contamination period, considerable uncertainty is associated with the predictions. Some of the uncertainty was characterized when ATSDR performed statistical analyses to calculate the probability that its exposure estimates were reasonable. To gain some perspective on its estimates, ATSDR compared its monthly estimates with the U.S. Environmental Protection Agency (EPA) maximum contaminant level (MCL) for PCE in drinking water of 5 µg/L that was established in 1985. The model estimated that starting in No-

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vember 1957, the concentration of PCE delivered to residents exceeded that MCL and remained well above it until the wells were closed in 1985.

The committee concluded that ATSDR applied scientifically rigorous approaches to address the complex groundwater-contamination scenario at Tarawa Terrace. The outcome of the modeling was monthly estimates of the concentrations of contaminants in the water supply to which people could have been exposed. Although ATSDR recognized and tried to account for the limitations and uncertainties associated with its models, the committee judges that—because of the sparse set of water-quality measurements, the need to make unverifiable assumptions, and the complex nature of the PCE source—it is virtually impossible to estimate exposure to historical levels of PCE and its degradation products accurately. Reporting precise values based on model predictions gives the misleading impression that the exposure of the former residents and workers at Tarawa Terrace during specific periods can be accurately defined. It is the committee's judgment that ATSDR's model is best used for estimating exposure categories qualitatively. From that perspective, a single exposure category of "exposed" appears to be applicable to persons who resided or worked at Tarawa Terrace during 1957-1985.

Hadnot Point

The water-supply contamination scenario for Hadnot Point is much more complex than that for Tarawa Terrace because there were multiple sources and contaminants. The extent of contamination has not yet been characterized, inasmuch as historical reconstruction or groundwater modeling has not yet been performed for Hadnot Point. The committee therefore relied on site descriptions of source areas, laboratory reports and other documentation of supply-water sampling, and results of monitoring of groundwater wells that were installed as part of remedial investigations to characterize likely exposures. Numerous sites have been identified as possibly contributing to the contamination of the groundwater, including an industrial area, a drum dump, a transformer storage lot, an industrial fly-ash dump, an open storage pit, a former fire training area, a site of a former on-base dry cleaner, a liquid-disposal area, a former burn dump, a fuel-tank sludge area, and the site of the original base dump. TCE appears to be the primary contaminant of concern on the basis of measurement data from the 1980s, but many other chemicals had the potential to contaminate the water supply, given the nature of activities at sites near the supply wells. Other chemicals measured in the water supply included PCE, vinyl chloride, 1,1-DCE, 1,2-DCE, methylene chloride, benzene, and toluene. Sampling performed in the early 1990s as part of remedial investigations also detected metals in monitoring wells, but little if any metal analysis was conducted for the timeframe of interest (1943-1985), and the committee did not review such data. Qualitative evidence suggests that the potential magnitude of groundwater contamination appears to have been much higher at Hadnot Point than at Tarawa Terrace.

ATSDR plans to perform a historical reconstruction of estimates of the concentrations of water-supply contaminants at Hadnot Point similar to the one performed for Tarawa Terrace. On the basis of its review of Hadnot Point water-system contamination, the historical groundwater modeling performed for Tarawa Terrace, and ATSDR's preliminary plans for historically reconstructing exposures that occurred at Hadnot Point, the committee recommends that simpler models be used instead of complex groundwater models. In particular, the use of conceptual models based on hydrogeologic characterization studies coupled with mass-balance calculations or analytic models should be given serious consideration because they can be performed relatively quickly and can be used to achieve a crude characterization of the degree and timeframe of contamination of the aquifer. Groundwater-modeling studies using public-domain MODFLOW-family tools should be performed only after establishing a clear need for a study. To support further analyses, the committee also recommends that the Marine Corps create and maintain a comprehensive public database of water-quality measurements for all environmental media samples collected across the base in the course of investigating the nature and extent of contamination at Camp Lejeune. The database should include information on where samples were taken, sampling dates, analytes meas-

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ured, laboratory quality-control information (including limits of detection), and other information relevant to exposure assessment.

Water-Use Patterns and Behavior

Places and dates of residence are key determinants of likely exposure at Camp Lejeune, but individual behaviors also affect the magnitude of exposure. Such behavior includes water consumption, showering or bathing patterns, and other water-related behavior (such as dishwashing). Such information is not available in archival records, and it is far too remote in time for accurate recall. A study in progress evaluating birth defects and childhood cancers is collecting self-reported water-use information from surviving mothers of offspring in the study, but the data are not yet available. The contaminated water systems also supplied nonresidential areas of the base, including schools, workplaces, recreational areas, and a hospital. Water-use patterns and behavior in those setting are expected to differ substantially from residential uses and behavior. In addition, the residential and nonresidential exposures could overlap, and people could have been exposed to contaminated water at multiple locations.

HEALTH-EFFECTS EVALUATION

The committee considered a wide spectrum of potential health effects that are known or suspected to be associated with TCE and PCE by surveying the scientific literature on the contaminants and the health problems reported by former residents and workers of Camp Lejeune. The scientific literature reviewed included reports of toxicologic experiments with the solvents in laboratory animals; of epidemiologic studies of workers and communities exposed to TCE, PCE, and mixed solvents; and of studies of the Camp Lejeune population. Studies on how the chemicals are processed and distributed in the body of laboratory animals and humans were also reviewed and compared. Those lines of research were considered separately and then considered together to determine the health outcomes that were of greatest concern. The health effects on which there was convergent information from the toxicologic and epidemiologic literature, even if not perfectly concordant, were considered by the committee to be of most interest.

Epidemiologic Evidence

In evaluating the epidemiologic literature, the committee adopted a categorization scheme developed by the Institute of Medicine (IOM) for determining whether data indicate a statistical association between chemicals and various health outcomes. IOM's approach was developed to evaluate exposure of veterans of the Vietnam War and the Gulf War and is used by the Department of Veterans Affairs to make decisions about compensation. The five categories in the scheme are limited/suggestive evidence of no association, inadequate/insufficient evidence to determine whether an association exists, limited/suggestive evidence of an association, sufficient evidence of an association, and sufficient evidence of a causal relationship. Among the five categories, only two were judged to be applicable to the literature on TCE and PCE: *limited/suggestive evidence of an association* and *inadequate/insufficient evidence to determine whether an association exists*. In the category of limited/suggestive, the evidence suggests an association between exposure to a chemical and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, so there is incomplete support of any association and insufficient basis for inferring a *causal* association. In the category of inadequate/insufficient, the available evidence is of insufficient quantity, quality, or consistency to support a conclusion about the existence of an association.

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Overall, the committee did not find sufficient evidence to justify causal inference for any of the health effects it reviewed. The committee concluded that there was limited/suggestive evidence of an association between chronic exposure to TCE or PCE and cancers of the breast, bladder, kidneys, esophagus, and lungs. The epidemiologic literature was also judged to provide limited/suggestive evidence of an association between TCE or PCE and hepatic steatosis and acute tubular necrosis related to chronic exposure at high concentrations but not to chronic exposure at low concentrations. Studies also showed some evidence of an association between solvent exposure and acute glomerulonephritis. Findings of human studies were not sufficiently consistent to draw any firm conclusions about reproductive outcomes, but a few studies showed a potential association with male infertility, and there was a suggestion of an association between solvents in general and reduced fermale fecundability (the ability to conceive). The epidemiologic evidence provides some indication that solvent exposure during but not before pregnancy is associated with increased risk of miscarriage but not with preterm birth or reduced birth weight, and there is no direct evidence on perinatal mortality. The epidemiologic evidence on paternal exposure to TCE and adverse pregnancy outcome was inadequate/insufficient to determine whether an association exists. Human evidence on chronic exposure to TCE or PCE and the risk of congenital malformations was also judged to be inadequate to support conclusions about associations. Overall, there was limited/suggestive evidence of an association between principally inhalation exposure to solvents and neurobehavioral outcomes, with the most support for effects on visuomotor and motor function, fatigue, headache, and deficits in concentration; most of these effects were reported concurrently with exposure, and there has been little study of whether effects persist after exposure ceases. Epidemiologic studies have provided some support of two immunologically mediated outcomes—chronic glomerulonephritis and scleroderma. In each case, there is limited/suggestive evidence of an association with mixed solvent exposure and, for scleroderma, some indication of an association specifically with TCE.

Toxicologic Evidence

Animal cancer studies of TCE at maximally tolerated doses revealed liver and lung cancers in mice and kidney and testicular cancers in male rats. Similar cancer studies of PCE exposure revealed liver cancers in mice and mononuclear-cell leukemia and kidney cancer in male rats. These tumors were in most instances species-, gender-, and strain-specific. Malignant liver tumors were seen in only one strain of one sensitive species, the $B6C3F_1$ mouse. Studies revealed that metabolic and mechanistic similarities between rodents and humans are such that highly exposed workers might develop TCE- and PCE-induced kidney tumors but appear to be much less susceptible than rats.

Review of noncancerous health outcomes in studies of TCE and PCE exposure indicated increased lung toxicity in mice, and hepatic and renal toxicity was reported after high exposure in rodents. Metabolism of TCE and PCE in rodents is qualitatively similar to that in humans but is quantitatively different and results in greater susceptibility of rodents to these compounds. Other studies revealed that rodent liver, kidney, and lung cells are more sensitive than equivalent human cells. Toxicologic studies reported adverse effects on indicators of male fertility in rats and mice exposed to TCE and PCE, respectively, at high doses, but there was little evidence of female infertility even at high concentrations. The toxicologic data constitute strong evidence that neither solvent is associated with congenital malformations in rats. Adverse pregnancy outcomes were not seen in toxicologic studies of maternal exposure to TCE in rats. A reduction in number of litters and increased perinatal mortality were observed in studies of mating pairs of rats and mice. Pregnancy outcomes after maternal inhalation exposure of rats to PCE indicate a reduction in intrauterine growth. Auditory deficits, reduction in performance of tasks, and other neurologic effects were reported in rats exposed to high TCE concentrations. Changes in visual evoked potentials in rabbits and decreased wakefulness in rats were reported in response to inhalation exposure to TCE. A few studies have reported neurobehavioral changes and altered brain neurochemistry in rats in response to inhalation exposure to PCE. TCE caused allergic sensitization in animal studies, including contact dermatitis and exacerbation of asthma. Toxicologic studies have shown exacerbation of autoim-

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mune diseases in a genetically modified mouse model and immunosuppression after TCE exposure. Inhalation of PCE reduced innate bactericidal activity in mice subjected to inhaled microorganisms, but little information was available on the potential of PCE to suppress the immune system or to induce autoimmune diseases.

Integrated Consideration of the Epidemiologic and Toxicologic Evidence

Convergence of the epidemiologic and toxicologic evidence was considered to identify health outcomes of greatest interest and plausibility as potential consequences of exposure to TCE and PCE in the water supply. This approach supplemented IOM's categorization approach by explicitly considering how the toxicologic evidence adds to the weight of evidence in characterizing health risks posed by TCE and PCE. The complementary strengths and weaknesses of the two bodies of literature provide important information on outcomes that are most deserving of attention. Review of epidemiologic studies of cancer outcomes provides limited/suggestive evidence of an association between chronic exposure to TCE or PCE and cancers of the breast, bladder, kidneys, esophagus, and lungs. Among those outcomes, positive concordance with the toxicologic evidence was strongest for kidney cancer observed in workers exposed to TCE, sometimes at doses where acute neurotoxicity was observed.

For noncancer outcomes, some convergence was found for toxic effects on the liver and kidneys of rodents and humans. Rodents exposed to high concentrations of TCE and PCE exhibited hepatic damage and renal tubular-cell damage. Epidemiologic studies also found limited/suggestive evidence of an association with hepatic steatosis (fatty accumulation in the liver) and sensitive measures of acute renal tubular necrosis. Such damage was associated with chronic high-level exposure to solvents but not with chronic low-level exposure.

Separate toxicologic evidence and epidemiologic evidence of associations between exposure to solvents and reproductive outcomes were found, but there was little convergence for specific reproductive outcomes. For example, toxicologic studies of high doses have reported adverse effects on indicators of male fertility in rats exposed to TCE and mice exposed to PCE; human studies were not consistent enough to support any firm conclusions, but a few studies showed a potential association with male infertility. The human data on female fertility were suggestive of an association between solvents and the ability to conceive, but there was little evidence of an association in the toxicologic literature to support female infertility even at high doses. Although the epidemiologic evidence of an association between chronic exposure to TCE or PCE and congenital malformations was judged to be inadequate to support conclusions, the toxicologic data provide strong evidence that neither solvent is associated with congenital malformations in rats. Reduction in fetal weight after maternal exposure of rats to PCE was observed in one toxicologic study; this outcome is considered somewhat analogous to the human outcome of "small for gestational age" (SGA), for which the epidemiologic data are inadequate/insufficient for determining whether an association exists.

Toxicologic studies report effects of exposure to high doses of TCE on the nervous system, such as central nervous system depression, attention deficits, alterations in visual evoked potentials, and other neurologic outcomes. Neurologic effects in toxicologic studies of PCE include anesthetic effects at high doses and changes in behavior and neurochemical markers at lower doses. Epidemiologic studies provide limited/suggestive evidence of an association between inhalation exposure to solvents and neurobehavioral effects; most of the reported effects were concurrent with exposure, and there has been little study of whether neurobehavioral effects persist after exposure ends.

Regarding effects on the immune system, toxicologic studies in sensitive strains of mice indicate that TCE can act as a skin sensitizer, modulate existing asthma, produce immunosuppression, and influence autoimmune diseases. Immunotoxic data on PCE are less abundant, with only a suggestion of effects on allergic sensitization and immunosuppression. Epidemiologic studies show limited/suggestive evidence of an association between mixed solvent exposure and two immunologically mediated outcomes,

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chronic glomerulonephritis and scleroderma. There is some indication of a specific association between TCE and scleroderma.

The committee is aware that some other health outcomes reported by former residents of the base (for example, male breast cancer and second-generation effects) are not cited above. The absence of inclusion of specific health outcomes does not mean that such effects should be excluded from further consideration of the Camp Lejeune population. Rather, it indicates that those outcomes have not been specifically investigated, or if they were considered, the studies were too small or of insufficient quality to support inferences.

Exposure Estimates in the Context of the Toxicologic and Epidemiologic Evidence

Perspective is needed in evaluating the exposures that occurred at Camp Lejeune. For example, some exposures are described as being "high" and others as being "low." To understand the meaning of those descriptors, it is important to understand what is being compared. For example, ATSDR compared exposures with EPA's MCL of 5 µg/L for PCE. In 1985, EPA classified PCE as a probable human carcinogen, and its policy is to assign a public health goal of zero exposure for such chemicals. The analytic feasibility of measuring PCE was considered in the setting of the MCL, and 5 µg/L was selected because it was judged to be the lowest concentration that could be reliably detected. Thus, the MCL is not based on toxicologic or epidemiologic data.

In epidemiologic studies, "high" exposures tend to occur in occupational situations where TCE and PCE are used routinely. Inhalation is usually the primary route of exposure in occupational scenarios, with skin exposure a less important route. Exposure tends to be much lower in community studies than in occupational studies and to involve exposure by the oral, dermal, and inhalation routes.

In toxicologic studies, exposure is usually expressed in terms of vapor concentration for inhalation exposure (parts per million) and dose for oral exposure (milligrams per kilogram of body weight per day). Lowest-observed-adverse-effect levels (LOAELs) were identified from the animal toxicologic studies for different adverse health effects. In some cases, a no-observed-adverse-effect level was also identified. The committee compared LOAELs with a range of estimated daily intakes that may have occurred at Camp Lejeune. Adverse health outcomes used in the evaluation were renal toxicity, renal cancer, neurotoxicity, and immune-related health effects—adverse outcomes in animals judged to be most relevant to humans on the basis of metabolic, mechanistic, and epidemiologic studies. Because of known variation in contaminant concentrations at Camp Lejeune, the range of exposures considered included the highest measured concentrations of TCE and PCE in finished water, half those concentrations, and twice those concentrations. Results of a toxicologic hazard evaluation[1] indicate that the lowest doses that elicited adverse health effects in animals are much greater than the doses to children and adults that may have occurred, as estimated from the highest measurements taken of the Camp Lejeune water supplies. Thus, in the context of human occupational and animal studies, potential exposure of human populations at Camp Lejeune is described as being "low." Although such comparisons afford a general frame of reference, they should be considered as just one facet of the health-effects evaluation. There are limitations in extrapolating the results of toxicologic studies, in which laboratory animals are exposed to high concentrations under controlled conditions, to human exposure scenarios where exposure varies in concentration and duration. Even community studies cannot be directly extrapolated to the Camp Lejeune population, because the Camp Lejeune population was much more transient than the nonmilitary populations studied in the other scenarios; moreover, other contaminants or other risk factors were probably present in both cases.

[1]A dissenting viewpoint on the conduct of this evaluation is provided in Chapter 4.

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Past and Current Studies of the Camp Lejeune Population

Two analyses of the Camp Lejeune population have been completed by ATSDR, both of which focused specifically on health risks to children who were exposed in utero and considered measures of fetal growth and duration of gestation. No clear associations were found between exposure and mean birth weight, preterm birth, and SGA, although one study conducted a subgroup analysis and reported an increased risk of SGA in infants born to older mothers or mothers who had prior fetal losses. Weaknesses in both studies limit the ability to draw definitive conclusions—most important, weaknesses in exposure assessment. Place of residence at the time of birth was used to categorize people as exposed or unexposed despite the potential for migration in or out over the course of pregnancy. It was discovered after the study was completed that an area that was considered unexposed (Holcomb Boulevard) had received water from a contaminated system (Hadnot Point) for the first 4 years of the study period, so the study results became invalid. ATSDR plans to reanalyze its study with corrected exposure information; the committee views this as a useful effort that can be completed rapidly without awaiting water-modeling results.

An ATSDR study of the effect of prenatal exposure on birth defects and childhood cancers is under way. In addition to many of the same methodologic concerns as in the studies of fetal growth and preterm birth, the current study has limited statistical power to detect associations with congenital defects or childhood cancer, and it does not consider exposures in infancy or early childhood. The results of that study await completion of ATSDR's water modeling at Hadnot Point. As noted above, the committee recommends that simpler or conceptual groundwater modeling be performed for the analysis of Hadnot Point and that the results of that effort be applied to the completion of the case-control study of congenital defects and childhood cancer.

Future Studies of the Camp Lejeune Population

ATSDR has evaluated the feasibility of conducting three additional studies of the Camp Lejeune population, including a health survey and studies that would evaluate deaths from all causes and cancer incidence among former residents and workers. ATSDR identified some of the same diseases and disorders identified in the committee's review as being of interest. These included kidney cancer, lung cancer, breast cancer, scleroderma, liver disease, kidney disease, and spontaneous abortion. ATSDR also identified additional outcomes of possible interest for its study.

The proposed health survey was generated in response to a congressional directive. The survey would seek information on residential history and various health outcomes, and could be used to support the other two studies. The survey's success depends on getting adequate participation (at least 60%). Even if satisfactory participation is achieved, there are concerns that there could be bias in the reported data, because people who have experienced disease or illness are more likely to participate in the survey.

There are a number of difficulties with performing the mortality and cancer incidence studies, including identifying, locating, and recruiting the study participants and obtaining reliable health information on them in an efficient manner. The committee found that although ATSDR considered the major issues bearing on the feasibility of the studies and proposed reasonable approaches to address them, there remain serious, unresolved questions about the feasibility and ultimate value of the studies. For example, it is not clear that the cancer incidence study could be performed successfully, because it is contingent on the cooperation of many state cancer registries. Even with cooperation, the statistical power to compare groups of interest across the range of outcomes has yet to be assessed. Statistical power is also an issue with the mortality study. The quality of exposure assessment remains problematic as well. On the basis of information reviewed, the committee considers it unlikely that the proposed studies, even if the notable uncertainties about feasibility are all resolved favorably, will produce results of sufficient certainty to resolve the question of whether Camp Lejeune residents suffered adverse health effects from contaminated water.

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OVERARCHING CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- The available scientific information does not provide a sufficient basis for determining whether the population at Camp Lejeune has, in fact, suffered adverse health effects as a result of exposure to contaminants in the water supplies. On the one hand, several lines of scientific reasoning suggest such effects are unlikely to have occurred. The evidence includes a substantial body of research on the toxicology of TCE and PCE that indicates that the exposures required to cause adverse effects in laboratory animals were much larger than the highest measurements available on the Camp Lejeune water supplies; evidence that humans have lower sensitivity to TCE and PCE than rodents; epidemiologic data largely from occupational settings with higher, longer-term exposures to TCE and PCE that has not generated compelling evidence of adverse health effects; and the relatively short-term, intermittent nature of the exposures incurred at Camp Lejeune. On the other hand, the possibility that health effects may have been produced by the contaminant exposures at Camp Lejeune cannot be ruled out. Some effects of TCE or PCE exposure might have occurred below the level of detection in toxicologic studies, which focused on single contaminant exposures at high doses, used genetically homogeneous animal strains, and necessarily involved extrapolation across species. In addition, the population exposed at Camp Lejeune is more diverse and possibly more susceptible than those that have been exposed to TCE and PCE in occupational settings, and the actual concentrations of PCE and TCE and the presence of additional water contaminants are poorly documented and could thus be higher or more complex than the limited historical measurements suggest. There were divergent views among the committee members about the probability that each would assign to whether adverse health effects have in fact occurred, but there was consensus among them that scientific research is unable to provide more definitive answers to that question.
- Additional research on potential health effects of water contamination at Camp Lejeune are unlikely to provide definitive information on whether exposure to it resulted in adverse health effects. Limitations in population size, data availability, and data quality cannot be overcome. Those limitations are due in part to the lack of documentation of exposure and the difficulty in assessing the health events that residents experienced after they were exposed. Even if ATSDR's planned work goes forward successfully, the outcome of the efforts is unlikely to determine conclusively whether Camp Lejeune residents were adversely affected by exposure to water contaminants.
- Because of the historical and complex nature of the contamination that occurred at Camp Lejeune and the availability of few empirical data on concentrations in water supplies, only crude estimates of exposure can be obtained. Even with the use of reasonable and, in some cases, advanced approaches, limitations in data availability and quality cannot be overcome. Thus, only a general conclusion can be drawn that the Tarawa Terrace and Hadnot Point water-supply systems were contaminated and that residents and workers were exposed to the contaminants in a highly variable manner. Additional work should make it possible to assign exposure categories of exposed and unexposed based on time and residence with reasonable certainty.

Recommendations

Additional research on the affected population should be only one of several potential responses by the Marine Corps to the water-contamination at Camp Lejeune. Given the likelihood that such studies would extend for many years and their expected inability to deliver definitive information on whether the water-supply contamination at Camp Lejeune caused adverse health effects, efforts to address and resolve the concerns associated with the documented contamination should not be deferred until such research is completed. Policy changes or administrative actions that would help to resolve the controversy should proceed in parallel with the studies (if they are continued) rather than in sequence.

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1

Introduction

Camp Lejeune is a U.S. Marine Corps base that covers about 233 square miles in Onslow County, North Carolina. It was established in the early 1940s and is the site of six major Marine Corps commands and two U.S. Navy commands, including reconnaissance, intelligence, infantry, artillery, and amphibious units. In the early 1980s, the Marine Corps discovered that the drinking-water systems that supplied two areas of housing at Camp Lejeune (Tarawa Terrace and Hadnot Point) were contaminated with volatile organic compounds (VOCs). The major contaminants of concern were identified as the solvents trichloroethylene (TCE) and perchloroethylene (PCE).[1]

Investigation into the drinking-water contamination began in 1980, when a routine test was conducted for trihalomethanes, which are produced as byproducts of water-treatment processes. Results indicated that other contaminants were present, including TCE, PCE, and other VOCs. Further investigation revealed that wells serving Tarawa Terrace were contaminated with PCE from an off-base dry-cleaning operation because of accidental spills and improper disposal of PCE. The contamination probably began when dry-cleaning operations began in 1953 (Maslia et al. 2007). The wells serving the Hadnot Point water system had multiple sources of contamination and multiple contaminants, the most important of which was TCE. Sources of the contamination included on-base spills at industrial sites and leaks from underground storage tanks and drums at dumps and storage lots. The Hadnot Point water-treatment plant began operating in 1943, but no estimates have yet been made of when the contamination might have begun. The contaminated wells in both systems were removed from service during 1984-1985.

The residential areas served by the Tarawa Terrace and Hadnot Point water systems consisted primarily of enlisted-personnel family housing and barracks for unmarried service personnel. Thus, many of the exposed were young members of families and people of reproductive age. Both water systems also served base administrative offices, schools, and recreational areas. In addition, the Hadnot Point water system served the base hospital and an industrial area, periodically supplemented water supply to the Holcomb Boulevard system in summer months (Bove and Ruckart 2008), and temporarily supplied water to the Holcomb Boulevard water system for a 2-week period during an emergency in 1985 (GAO 2007). The number of people that lived or worked in the areas served by the contaminated water systems has not yet been determined.

There has been considerable controversy over the drinking-water contamination at Camp Lejeune. Questions have been raised about when the contamination was discovered, whether appropriate action was taken by the Marine Corps and the Department of the Navy (the department under which the Marine Corps operates), and whether information about the contamination was disclosed in timely and appropriate ways. Some people who became ill or whose families or friends became ill or died have sought to learn whether the contaminated drinking water might be to blame. They have also questioned whether the investigations that were conducted were the most appropriate ones and whether studies that

[1]PCE is also known as tetrachloroethylene or Perc.

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are under way will answer their questions definitively. Hundreds of former residents and employees of Camp Lejeune have filed claims with the Department of the Navy.

Several investigations have been performed on issues related to the discovery of the contamination at Camp Lejeune. A brief overview of the investigations follows.

INVESTIGATIONS

Camp Lejeune Studies

Health Investigations

A sequence of health investigations and studies were conducted by the Agency for Toxic Substances and Disease Registry (ATSDR) after the U.S. Environmental Protection Agency (EPA) added Camp Lejeune to its National Priorities List in October 1989. A public-health assessment evaluated exposures and potential risks at three sites on the base, including the sites served by the contaminated drinking-water systems (ATSDR 1997a). ATSDR judged that exposure to VOCs in drinking water was unlikely to pose health risks to adults but raised questions about risks to children who may have been exposed in utero. A followup study found no overall association between exposure and pregnancy outcome but reported that male infants were small for their gestational age (ATSDR 1998). Similarly, Sonnenfeld et al. (2001) found no overall association with pregnancy outcome but reported that infants of some groups of mothers who were exposed during pregnancy had lower birth weights.

ATSDR is now studying children born at Camp Lejeune in 1968-1985 to determine whether exposure to VOCs in drinking water is related to specific birth defects and childhood cancers. Health effects under consideration include spina bifida, anencephaly, cleft lip, cleft palate, childhood leukemia, and childhood non-Hodgkin lymphoma. The study will also include modeling of the contaminants and water-supply systems in an attempt to provide better estimates of which study participants might have been exposed and at what concentrations. The water modeling conducted to date and ATSDR's health studies are evaluated in Chapters 2 and 8, respectively.

Other Investigations

Several federal inquires on the contamination of the water supplies at Camp Lejeune were conducted. The inquiries were not health investigations or evaluations of scientific issues but rather were focused on activities surrounding the discovery and handling of the situation. A short summary is presented here to give the reader some background, but the issues are outside the scope of the current report and the investigations were not used or evaluated by the committee. One inquiry was conducted in 2004 by a panel chartered by the Marine Corps to review the facts surrounding the discovery of the drinking-water contamination and actions taken (Drinking Water Fact-Finding Panel for Camp Lejeune 2004). The panel found that the Marine Corps responded appropriately with the information available and found no evidence that an attempt was made to cover up evidence of the contamination. However, the panel concluded that the Navy should have been more aggressive in providing technical expertise to the Marine Corps so that it could understand the significance of the contamination, that communication between Camp Lejeune officials and between base officials and Navy technical support was not always adequate, and that communication with former residents did not provide enough details to characterize the contamination fully.

EPA conducted two inquiries. One, completed in 2005, was the EPA Office of Inspector General's investigation into complaints about EPA's response to Freedom of Information Act requests about the Camp Lejeune contamination and other issues regarding EPA's responsibilities. The Office of Inspector General found that EPA's responses to the information requests were not handled appropriately but

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also found that the other complaints were without merit or were outside the purview of EPA. The second EPA inquiry was conducted in 2003-2005 by its Criminal Investigation Division, which sought to determine whether any violations of federal laws had occurred, reasons for funding delays, and whether records and data were falsified or mishandled. The division was critical of some actions taken by Marine Corps and Navy officials but found that no federal laws were violated. The case was also forwarded to the Department of Justice for evaluation, which decided not to seek criminal prosecution.

The U.S. Government Accountability Office (GAO 2007) also assessed activities related to drinking-water contamination at Camp Lejeune. In its report to Congress, GAO described efforts to identify and address the contamination, activities that resulted from the discovery of the contamination, the government's actions, and the design of the current ATSDR study.

Contaminant Studies

The two drinking-water contaminants of greatest concern—TCE and PCE—are environmental contaminants used in occupational settings and commonly found at hazardous-waste sites. The two solvents have similar metabolites that are thought to be largely responsible for the toxicity observed after exposure. Studies have shown that TCE and PCE can have a number of adverse health effects, including cancer, when animals are exposed under experimental conditions. Epidemiologic studies of workers exposed to the solvents in occupational settings have been conducted, and there is a growing body of literature on community exposures to TCE and PCE in drinking water. In addition, several federal and state agencies have conducted or are conducting human health risk assessments or analyses of TCE and PCE. For example, ATSDR has released toxicologic profiles of TCE (ATSDR 1997b) and PCE (ATSDR 1997c), the International Agency for Research on Cancer has an evaluation of dry-cleaning and chlorinated solvents (IARC 1995), the California Environmental Protection Agency has a public-health goal for PCE in drinking water (Cal EPA 2001), and EPA is updating its human health risk assessments of TCE and PCE.

The Institute of Medicine (IOM 2003) performed a comprehensive assessment of the long-term adverse health outcomes associated with exposure to various solvents as part of its evaluation of agents to which Gulf War veterans were exposed, including TCE and PCE. The literature used in the IOM assessment consisted primarily of occupational studies of workers chronically exposed to solvents. Few of the studies included women or children. Animal data were used for making judgments about the biologic plausibility of associations but were not used as part of the weight-of-evidence approach.

In 2006, the National Research Council published *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues* (NRC 2006); it was based on a study sponsored by EPA, which was seeking guidance on updating its risk assessment of TCE. The report examined issues critical for developing an objective, scientifically based health risk assessment of TCE. As indicated above, EPA has not yet released a revised risk assessment of TCE.

COMMITTEE'S TASK

At the request of Congress, the Navy sponsored this study by a committee of the National Research Council to review the scientific evidence on associations between adverse health effects and historical data on prenatal, childhood, and adult exposures to contaminated drinking water at Camp Lejeune, North Carolina. The committee was asked to assess the strength of evidence in establishing a link or association between exposure to TCE, PCE, and other drinking-water contaminants and each adverse health effect suspected to be associated with such exposure. For each health effect reviewed, the committee was to determine, to the extent practicable with the available scientific data, whether a statistical association between contaminant exposure and the health effect exists, whether a plausible biologic mechanism or other evidence of a causal relationship between contaminant exposure and effect exists, the strength of

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evidence for a causal inference for each health effect, and other scientific considerations that may help the Navy to set priorities for future activities.

The committee's review was to include an evaluation of the toxicologic and epidemiologic literature on adverse health effects of TCE and PCE, including studies of populations exposed to similar concentrations of the contaminants of concern; risk-assessment reports from government agencies; recent literature reviews by the National Research Council, IOM, and other groups; completed and current ATSDR studies at Camp Lejeune; and published meta-analyses. In its evaluation of previous and current health studies of residents of Camp Lejeune, the committee was asked to review the appropriateness of the study question, design, analysis, results, and conclusions.

COMMITTEE'S APPROACH

To address its task, the committee held two public meetings in September and November 2007 to gather information from the sponsor and other parties knowledgeable about the contamination and related issues. The Marine Corps made presentations on the drinking-water contamination at Camp Lejeune and addressed questions about the scope of work. Presentations were also made by ATSDR on its past and current health studies of former residents and on its current groundwater modeling activities to estimate the exposures that occurred historically at the base. GAO reported on its investigation into actions taken by various agencies in response to the discovery of the contamination. Representatives of ATSDR's community-assistance panel informed the committee about the panel's activities and about the specific health concerns raised by former residents. There were also open-microphone sessions to hear from former residents and employees of the base about their concerns and to learn about information that they had that was relevant to the study. The committee visited Camp Lejeune to get firsthand information on the affected housing areas; information on the location of wells, water-treatment plants, and base boundaries; and other site information to use in its evaluation. A third public meeting was held in September 2008 to hear about ATSDR's assessment of the feasibility of conducting additional epidemiologic studies.

The current report expands on previous reviews of the Camp Lejeune drinking-water contamination by providing an assessment of multiple lines of research to ascertain the likelihood that exposure to the contaminated water supply is associated with adverse health effects. The evidence reviewed included exposure evaluations performed by other organizations, raw data on the contaminants measured in the water supply, studies of contaminants in laboratory animals, studies of human populations exposed to the contaminants, and studies of the Camp Lejeune population.

As specified in the task, the committee also took advantage of the comprehensive literature reviews and health risk assessments that were performed by other agencies. The report by IOM (2003) figured prominently in the committee's evaluation of the epidemiologic evidence because it provided a comprehensive review of the epidemiologic research on TCE and PCE and individual health outcomes and categorized the evidence according to an established scheme accepted by the Department of Veterans Affairs in evaluating risks to veterans of the Vietnam War and the Gulf War. The committee updated IOM's review, modified categorizations where appropriate, reviewed literature on pregnancy outcomes in women exposed during pregnancy (a population excluded from IOM's review because pregnant women are not deployed), and expanded on IOM's approach by explicitly considering how evidence from the animal literature adds to the weight of evidence and by considering the exposures that were likely to have occurred at Camp Lejeune.

The committee also considered the possible contribution of additional research to inform Marine Corps decisions about what actions to take about the past water-supply contamination and its possible contribution to scientific knowledge. The committee approached that question by considering possible research activities, evaluating their feasibility, and assessing whether the results would substantively inform decisions by the Marine Corps or contribute to scientific knowledge.

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ORGANIZATION OF THE REPORT

The report first discusses the individual elements of the committee's review of the drinking-water contamination at Camp Lejeune (Chapters 2-7) and then considers the elements together to draw conclusions about whether particular health outcomes can be linked to the exposures that occurred. Chapter 2 evaluates what is known about the possible exposures of the populations that lived or worked in areas served by the contaminated water systems. On the basis of what is known about the primary contaminants of concern, Chapter 3 discusses some of the biochemical changes that occur after the contaminants enter the body and how they or their metabolic products are transported in the body; it also considers populations that might be more susceptible to effects of the contaminants, lifestyle factors that affect how the contaminants interact in the body, and how the contaminants interact with each other and with other chemicals in the body. In reviewing what adverse health effects might result from exposure to the contaminants, the committee first reviews the toxicology literature in Chapter 4, which involves primarily studying effects in animals given the contaminants under experimental conditions. Chapter 5 reviews studies of human subjects who were exposed to the same chemicals that contaminated the Camp Lejeune drinking-water system, mainly studies of occupational exposure. Chapter 6 evaluates studies of populations exposed to similar contaminants via drinking water to see whether any inferences that would be applicable to the Camp Lejeune situation can be drawn. The toxicologic and epidemiologic evidence is considered together in Chapter 7 to determine the strength of the available evidence on particular health outcomes. Chapter 8 deals specifically with studies of exposure and health effects in former residents of Camp Lejeune, including completed, current, and proposed studies by ATSDR.

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2

Exposure to Contaminants in Water Supplies at Camp Lejeune

This chapter describes the scenarios of exposure to contaminants in the water supplies at Marine Corps Base Camp Lejeune and identifies gaps in understanding of the exposures of people who lived or worked on the base while the water supplies were contaminated. First, exposure assessment for epidemiologic studies is discussed to set forth concepts that will be used in other chapters that review epidemiologic evidence (see Chapters 5 and 6). Then, an overview of the water-supply contamination scenarios at Camp Lejeune and important considerations for characterizing them are presented, including hydrogeologic features of the site, the base's water-treatment plants and distribution systems, contaminated areas, and water-quality measurements. Finally, information on the Tarawa Terrace and Hadnot Point water systems is evaluated.

EXPOSURE ASSESSMENT FOR EPIDEMIOLOGIC STUDIES

In public health, the term *exposure* refers to contact with an agent (such as environmental contaminant) that occurs at the boundary between a person and the environment. *Exposure assessment* can be defined as the qualitative or quantitative determination or estimation of the magnitude, frequency, duration, and rate of exposure of a person or a population to a chemical (ILSI 2000). Often, the focus is on identifying one or more exposure pathways and, for each exposure pathway, the source, the environmental medium through which the contaminant is transported and possibly transformed, the receptor (individual or population), how contact occurs, and the route of exposure. The goal is to determine how much of a contaminant is absorbed and at what rate (the dose) so that an assessment can be made as to whether the absorbed contaminant produced or might produce an adverse biologic effect (Lioy 1990). The possible routes of exposure are inhalation, if the contaminant is present in the air; ingestion, through food, drinking, or hand-to-mouth behavior; and dermal absorption, if the contaminant can be absorbed through the skin. In the field of exposure science, research has been focused on developing methods for quantifying the uncertainty and error in the exposure assessments and on correcting the assessments for such error or uncertainty when possible. New methods are being developed to account for cumulative exposure to multiple chemicals (ILSI 2000), as are probabilistic models for cumulative and aggregate exposure assessment (for example, Nieuwenhuijsen et al. 2006) and the application of exposure modeling based on geographic information systems (Nuckols et al. 2004; Mindell and Barrowcliffe 2005; Beale et al. 2008).

A well-designed epidemiologic study should have the capability to evaluate exposure in relation to an appropriate latent period of a disease and to evaluate critical windows of exposure. In most epidemiologic studies, exposure cannot be measured directly or completely, and surrogate information is used to classify study subjects into exposure groups. Good surrogates for exposure elucidate the variation

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in exposure in the study population while minimizing exposure misclassification (error). Misclassification of exposure is of particular concern in environmental-epidemiology studies because the health effects of environmental exposures tend to be small, and it is usually difficult to accurately estimate exposure to environmental contaminants, which can occur by multiple pathways and in multiple locations. Furthermore, environmental exposures are often at low concentrations, which make biases due to exposure misclassification more likely to affect epidemiologic results. If misclassification of exposure is not differential by health outcome, it commonly biases risk estimates toward the null (that is, toward finding no association) and can cause associations to be missed (Copeland et al. 1977; Flegal et al. 1986). To evaluate the degree of misclassification in an epidemiologic study, it is important to consider the ability of an exposure metric to correctly classify the magnitude of exposure in the study population and to differentiate between those who are exposed at magnitudes that could result in adverse health effects (sensitivity) and those who are exposed at lower magnitudes (specificity). It is important to maximize specificity when the prevalence of exposure in the study population is low and to maximize sensitivity when the prevalence of exposure is high (Nuckols et al. 2004).

Exposure assessment for epidemiologic studies of the effects of water-supply contamination includes two components. The first is estimation of the magnitude, duration, and variability of contaminant concentrations in water supplied to consumers. An important consideration is hydrogeologic plausibility: an association between a contaminant source and exposure of an individual or population cannot exist unless there is a plausible hydrogeologic route of transport for the contaminant between the source and the receptor (Nuckols et al. 2004). The second component is information on individual water-use patterns and other water-related behaviors that affect the degree to which exposures occur, including drinking-water consumption (ingestion) and dermal contact and inhalation related to the duration and frequency of showering, bathing, and other water-use activities. Water use is an important determinant of variability of exposure to water-supply contaminants, particularly if it varies widely in the study population. Ideally, exposure-assessment strategies include both components, but in practice it may be difficult to obtain either adequately.

A number of approaches have been used to assign exposures in studies of health effects of water-supply contamination. They have ranged from measures of exposure defined by geographic region or job classification (group-level or ecologic exposure) to more sophisticated measures that yield individual exposure estimates. Selecting an optimal approach for a given study is dictated in part by the epidemiologic-study design, the size and geographic extent of the affected population, and the quantity and quality of available exposure-related data. The approaches that have been used in epidemiologic studies of water-supply contamination are more fully described in Chapter 6. The following sections provide information on the water-supply contamination and exposure scenarios at Camp Lejeune.

WATER-SUPPLY CONTAMINATION AT CAMP LEJEUNE

In the early 1940s, the U.S. Marine Corps constructed a water-distribution piping system at Camp Lejeune. The source of water in the system was, and continues to be, groundwater wells. The water-treatment processes, distribution systems, and contributing wells have been modified to accommodate the additional demand due to population growth and to improve water quantity and quality. Four water systems—Hadnot Point, Tarawa Terrace, Marine Corp Air Station, and Holcomb Boulevard—have supplied water to most of the residences and workplaces (see Figure 2-1). Other water-distribution systems on the base are Onslow Beach, Courthouse Bay, Rifle Range, and Camp Johnson.

In late 1984 and early 1985, Marine Corps authorities removed a number of supply wells from service in the Tarawa Terrace and Hadnot Point systems after concluding that they were contaminated with solvents (GAO 2007). The sources of contamination of the two systems were different. Investigation into the source of perchloroethylene (PCE) contamination of the Tarawa Terrace water system concluded

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Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects

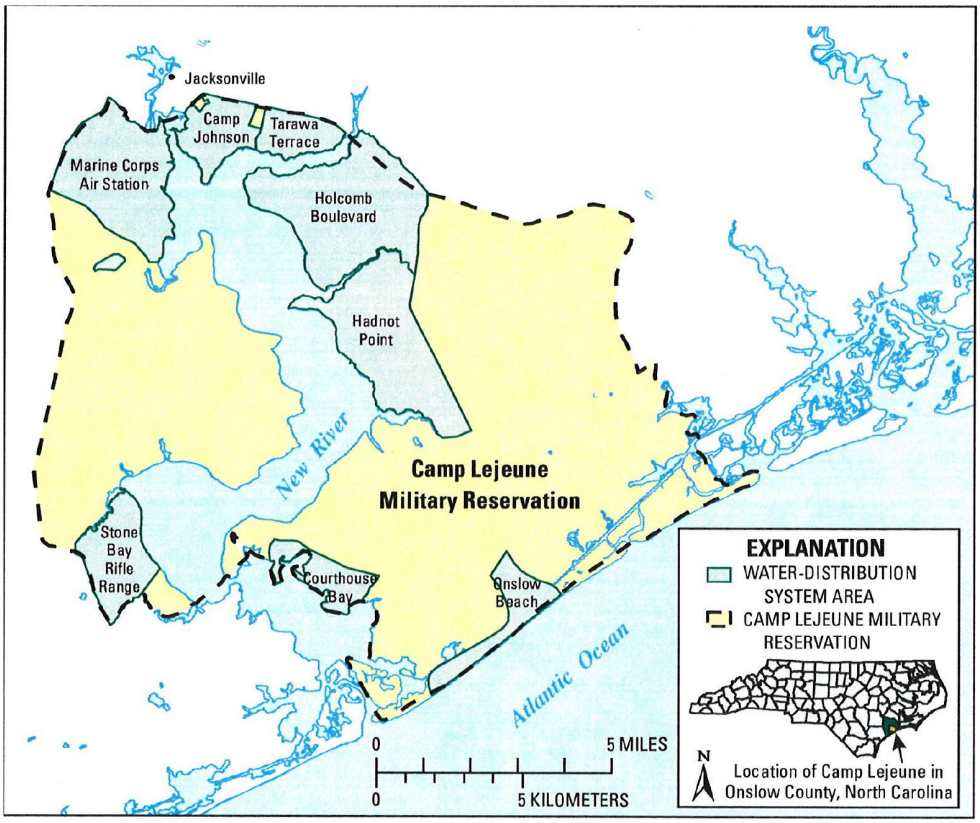


FIGURE 2-1 Water-distribution systems serving U.S. Marine Corps Base, Camp Lejeune, North Carolina. Source: Maslia 2005.

that it was due to waste-disposal practices at ABC One-Hour Cleaners, an off-base dry-cleaning facility (Shiver 1985). The dry-cleaning site was classified as a federal hazardous-waste site during March 1989 under the Comprehensive Environmental Response, Compensation, and Liability Act, commonly known as the Superfund Act, and remedial investigation began in 1990 (Faye and Green 2007). The Agency for Toxic Substances and Disease Registry (ATSDR) completed an extensive water-modeling study to predict the extent of contamination (spatially and temporally) in the period January 1951–January 1994 (Faye 2008; see discussion of the modeling later in this chapter). Quantitative estimates of contaminant concentrations in the water supply from that modeling effort will be used in current and planned ATSDR epidemiologic studies of the Camp Lejeune population.

A report from the U.S. Government Accountability Office (GAO 2007) states that the sources of contamination at Hadnot Point are uncertain but are likely to include many on-base sites, including landfills and base operations where solvents and other compounds were disposed of or used. ATSDR plans to do a historical reconstruction for the Hadnot Point water-distribution system to estimate the extent of groundwater contamination of wells and the extent to which water supplies of housing and public buildings served by this system were contaminated (M. Maslia, ATSDR, personal commun., March 12, 2008).

The committee is not aware of any extensive studies concerning potential contamination of wells serving other water-supply systems on the base. Those wells directly serve the Holcomb Boulevard, Marine Corps Air Station, Courthouse Bay, Camp Johnson, Camp Geiger, and Rifle Range water-supply systems and several smaller systems. Some water-supply systems are connected (for example, Holcomb Boulevard and Hadnot Point), and Bove and Ruckart (2008) documents some reports of intermittent delivery of water from the Hadnot Point system to the Holcomb Boulevard system.

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Hydrogeologic Features of Exposure at Camp Lejeune

On the basis of geophysical data and lithologic logs, several productive aquifers were found to exist beneath Camp Lejeune. The geologic cross-sectional details on the site, as reported in Harden et al. (2004), are summarized in Figure 2-2. The aquifers include the Castle Hayne aquifer and two other deep aquifers beneath the Beaufort confining unit, the Beaufort and Peedee aquifers. All the water-supply wells were installed within the Castle Hayne aquifer, so site characterization efforts focused on understanding the hydrostratigraphy of the upper three hydrogeologic units: the surficial aquifer, the Castle Hayne confining unit, and the Castle Hayne aquifer. Each unit is known to have multiple subunits that consist of seams of clay, silt, and sandy beds (as indicated in Figure 2-2). The sections below summarize the available hydrogeologic data for the three units.

Surficial Aquifer

The thickness of the surficial aquifer at Camp Lejeune ranges from 0 to 73 ft and averages about 25 ft (Cardinell et al. 1993). The largest observed thickness occurs in the southeastern part of Camp Lejeune. The aquifer consists of interfingered beds of sand, clay, sandy clay, and silt of both Quaternary and Tertiary age. The clay and silt beds that occur in the surficial aquifer are thin and discontinuous. The aquifer is often classified into several subunits; and the extent and depth of the subunits can vary among locations. For example, in the vicinity of Tarawa Terrace, three minor units have been identified in the surficial aquifer (the Brewster Boulevard unit, the Tarawa Terrace unit, and the Upper Castle Hayne River bend unit). Review of available cross-sectional hydrogeologic data does not indicate any distinct demarcation between the subunits; hence, they were conceptualized as a single surficial unit in groundwater-flow models (Faye and Valenzuela 2007). According to Winner and Coble (1989), the surficial aquifer is composed of more than 90% sand in the eastern part of the base and about 70-90% sand in the western part. The aquifer is directly recharged by infiltration from rainfall that ranged from 28 to 70 in/year during 1952-1994. Tant et al. (1974) found that the soils in Camp Lejeune have good infiltration capacity. Effective groundwater recharge is estimated to range from 6.6 to 19.3 in/year. The estimated average hydraulic conductivity of the surficial aquifer in the Camp Lejeune area is about 50 ft/day (Winner and Coble 1989). Conceptually, groundwater in the shallow surficial aquifer moves from areas of high hydraulic head in interstream divides toward areas of low hydraulic head at surface-water discharge areas (Harden et al. 2004).

Castle Hayne Confining Unit

The Castle Hayne confining unit lies beneath the surficial aquifer, and this clayey unit is conceptualized as the top confining layer of the Castle Hayne aquifer. However, the lithostratigraphic top of Castle Hayne aquifer is not continuous, and the thickness of the confining layer ranges from 0 to 26 ft, averaging about 9 ft where present. Harned et al. (1989) concluded that no continuous confining unit or clay bed appears to separate the surficial and Castle Hayne aquifers except in the easternmost side of the Hadnot Point area. Furthermore, the thickness and distribution of the confining clay layers observed in various cross sections summarized by Harned et al. (1989) and Cardinell et al. (1993) are similar. The thin (5-10 ft) and discontinuous clay layers observed in several cross sections indicate that the degree of hydrologic connection between the aquifers could be substantial (Harned et al. 1989). The vertical hydraulic conductivity of the confining material, where present, is estimated to range from 0.0014 to 0.41 ft/day (Cardinell et al. 1993).

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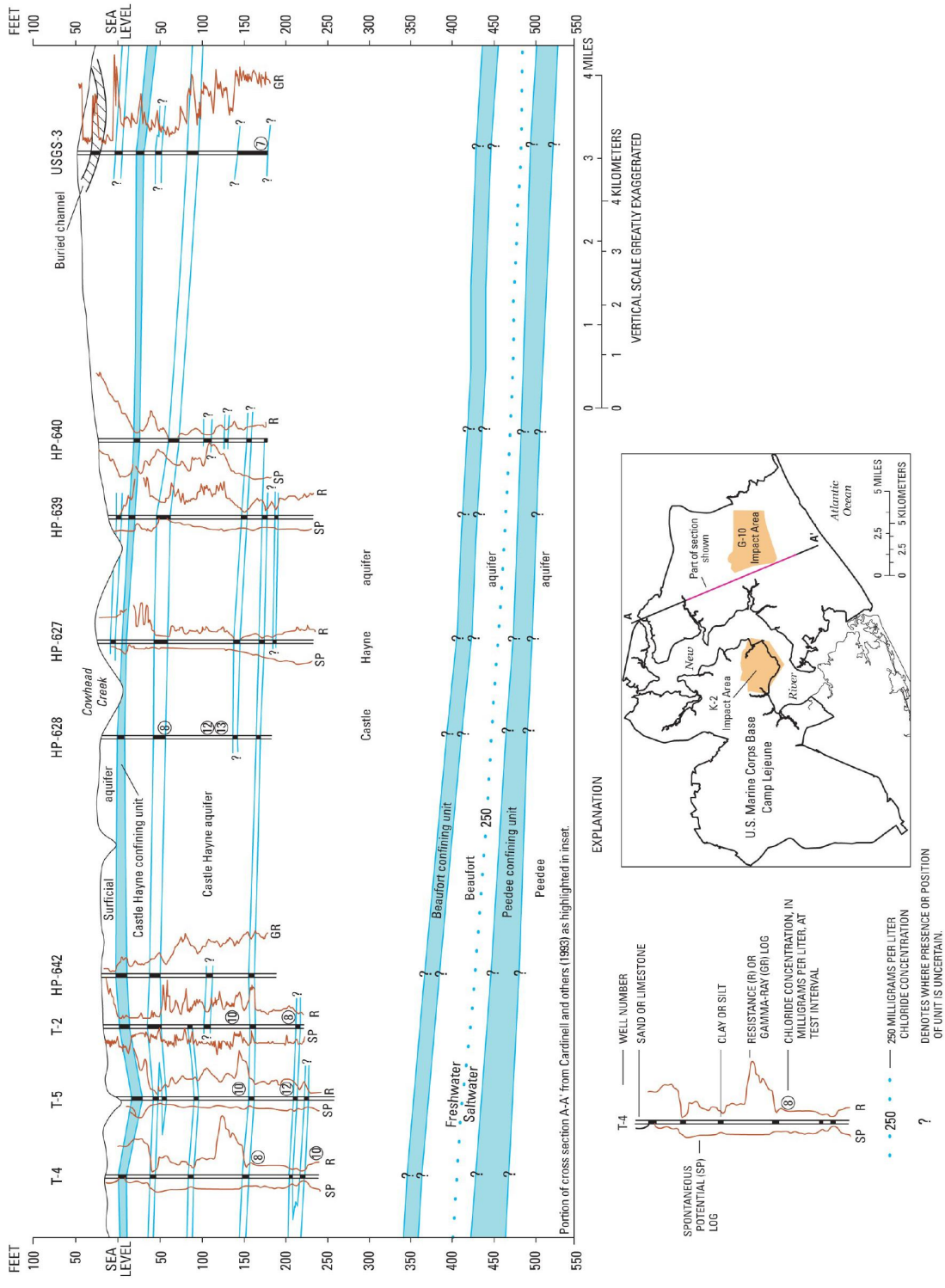


FIGURE 2-2 Geologic cross section of Camp Lejeune. Source: Harden et al. 2004.

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Castle Hayne Aquifer

The thickness of the Castle Hayne aquifer can range from about 200 to 400 ft. The aquifer is thinnest in the area of Camp Geiger in the northwest corner of the base and thickest in the eastern boundary. The bottom of the Castle Hayne aquifer is bounded by a regionally continuous clay unit, which is designated the Beaufort confining unit. All the groundwater-extraction wells in the base are in the Castle Hayne aquifer. The aquifer consists primarily of beds of sand, shell, and limestone (Winner and Coble 1989). The highly conductive material decreases from west to east across Camp Lejeune. The estimated hydraulic conductivity of the aquifer ranges from 14 to 91 ft/day (Cardinell et al. 1993). A portion of water from the surficial aquifer is able to infiltrate (move through or around) the upper confining unit, and this serves as the primary mechanism for recharging the Castle Hayne aquifer. Harned et al. (1989) also observed that in interstream areas the water level in the surficial aquifers can be 2-6 ft higher than the Castle Hayne aquifer and that the high vertical gradients can induce considerable vertical recharge. There is also some evidence of a potential for recharge of the Castle Hayne aquifer through the lower confining unit from the Beaufort aquifer (Cardinell et al. 1993). Finally, several paleostream channels have been identified within the Castle Hayne aquifer; these highly permeable, sandy channel beds can have considerable influence in local groundwater recharge, transport, and discharge patterns.

Characteristics of Source Zones

Predicting the dynamics of contaminant transport from contaminant source zones requires the use of groundwater models that simulate a complex set of fate and transport processes. Results from these models should be interpreted in light of a conceptual framework that integrates the chemical and geologic complexities in sources and receptors to establish a relationship between the contaminant source and the groundwater wells. An example of such a source-receptor conceptual model for a waste site contaminated with volatile organic compounds (VOCs) like PCE or TCE is illustrated in Figure 2-3.

At a typical waste site, spent VOCs are present in the unsaturated zone (a partially saturated soil layer above the water table) in the form of dense nonaqueous-phase liquids (DNAPLs). Pure-phase VOCs are DNAPLs that do not mix with water and have an "oily" texture. They can be trapped in soil pore spaces, and their dissolution (dissolving process) is limited by a complex set of mass-transfer processes (Miller et al. 1991; Jackson 1998; Clement et al. 2004b). Furthermore, considerable spatial variability in DNAPL mass distribution in a source region is almost inevitable; consequently, mass detection at DNAPL-contaminated field sites is extremely difficult and uncertain (Abriola 2005).

Laboratory-scale tank studies have indicated that under typical groundwater-flow conditions the DNAPL dissolving process will be limited by various mass-transfer processes, so concentrations of only about 10-20% of the maximum solubility level can be obtained (Clement et al. 2004a). Furthermore, waste DNAPLs, similar to the ones disposed of at Camp Lejeune, may mix with other chemicals that limit the mass-transfer kinetics further and lead to considerable reduction in solubility (Clement et al. 2002). Therefore, the presence of even a small volume of DNAPL can contaminate a large volume of groundwater for several decades as DNAPL continues to dissolve.

Figure 2-3 illustrates various possible pathways for groundwater contamination from a DNAPL source. If the quantity of the waste product (DNAPL) is high enough, the waste will migrate downward and penetrate the water table. The vertical migration will eventually cease, and the DNAPL will be trapped in the pore spaces or will pool over low permeable clay layers. The DNAPL phase will slowly dissolve into the water phase, and the dissolved plume will be transported toward the extraction wells. The migration patterns of DNAPL contaminants will also be highly influenced by local hydrogeologic conditions. The presence of low-permeability units (such as the Castle Hayne confining unit or any clay units) would limit vertical migration of both DNAPL and dissolved contaminants. At Camp Lejeune, all

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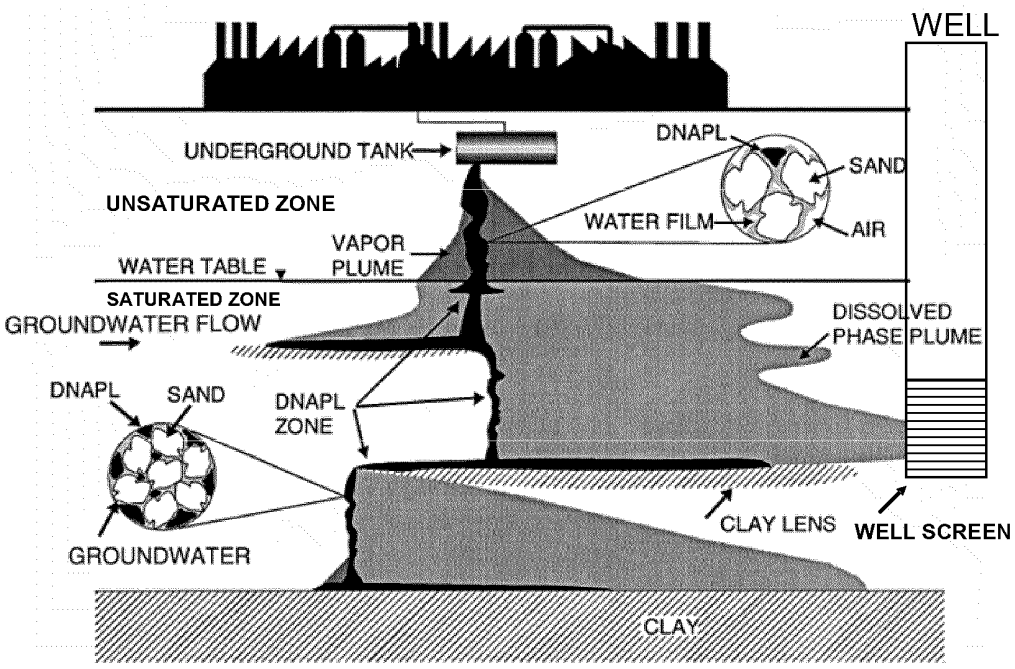


FIGURE 2-3 Conceptual model of DNAPL transport. The well is shown at an exaggerated scale. Source: Modified from Jackson 1998. Reprinted with permission; copyright 1998, *Hydrogeology Journal*.

the groundwater-supply wells are beneath the surficial aquifer. Therefore, the ability of the contaminants to reach the receptor (well screen) at the site depends on local groundwater gradients, on the thickness (or existence) and geometry of the low-permeability clay or silt zones between the source and the well, and on the geometry of the hydrostratigraphic units. The presence of a thick clay unit between the source and the receptor retards transport; however, strong pumping could induce vertical gradients and enhance contaminant transport.

Water-Treatment Plants and Distribution System

A chronology of the water-supply systems providing water to the residential areas at Camp Lejeune from 1941 to 2000 is presented in Table 2-1. At various times, four systems have been the primary sources of water for residences other than barracks at Camp Lejeune since the first system was put into service: Hadnot Point, Tarawa Terrace, Marine Corps Air Station, and Holcomb Boulevard. Several smaller systems have supplied or still supply other areas of the base that have relatively low populations. For each system, a set of supply wells pumped water to a centralized water-treatment plant, where the water was mixed before distribution to housing areas, public buildings (such as schools), businesses, and workplaces.

Figure 2-4 provides an illustration of a conceptual model of a water-supply system at Camp Lejeune. Water-supply wells collected groundwater and pumped it to the water-treatment plant when the wells were turned on. Not all the wells operated at the same time. The wells were "cycled," meaning that only a few wells pumped water to the treatment plant at any given time. Water from several wells was mixed at the treatment plant and processed before being distributed in the pipes that supplied water to the base. Limited historical information is available on the pumping schedules of the wells or the water-treatment techniques that were used.

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In general, the water-treatment processes used by the Marine Corps generally included coagulation, sedimentation, filtration (with sand or anthracite), and lime softening (Marine Corps, personal commun., May 22, 2008). The American Water Works Association (AWWA) reported that efficiency of removal of VOCs would be poor (0-20%) without lime softening and poor to fair (0-60%) with lime softening, of synthetic organic chemicals poor to good (0-80%), and of metals good to excellent (80-100%) except for chromium^{+6} (less than 20%) (AWWA 1995). Actual removal efficiencies are site-specific and depend on how each water-treatment plant is operated.

TABLE 2-1 Water Supply of Housing Areas, Camp Lejeune, North Carolina (1941-2000)

Housing Area	Water-Treatment Plant	Dates of Service
Family housing areas		
Courthouse Bay	Courthouse Bay	1942-2000
Berkeley Manor	Hadnot Point	1961-1971
	Holcomb Boulevard	1972-2000
Hospital Point	Hadnot Point	1947-2000
Knox Trailer Park	Tarawa Terrace	1952-1986
	Holcomb Boulevard	1987-2000
Knox Trailer Park Expanded	Holcomb Boulevard	1989-2000
Marine Corps Air Station	Marine Corps Air Station	1958-2000
Midway Park	Hadnot Point	1943-1971
	Holcomb Boulevard	1972-2000
Paradise Point Cape Cod	Hadnot Point	1948-1971
	Holcomb Boulevard	1972-2000
Paradise Point Capehart	Hadnot Point	1962-1971
	Holcomb Boulevard	1972-2000
Paradise Point Cracker Box	Hadnot Point	1947-1971
	Holcomb Boulevard	1972-2000
Paradise Point general officer housing	Hadnot Point	1943-1971
	Holcomb Boulevard	1972-2000
Paradise Point two-story housing	Hadnot Point	1943-1971
	Holcomb Boulevard	1972-2000
Rifle Range housing	Rifle Range	1942-1993
	Onslow County	1994-2000
Tarawa Terrace I and II	Tarawa Terrace	1952-1986
	Holcomb Boulevard	1987-2000
Watkins Village	Holcomb Boulevard	1978-2000
Barracks subcamps (not individual barracks)		
Camp Geiger	Camp Geiger	1941-1976
	Marine Corps Air Station	1977-2000
Camp Johnson	Camp Johnson	1941-1986
	Holcomb Boulevard	1987-2000
Courthouse Bay	Courthouse Bay	1941-2000
French Creek	Hadnot Point	1943-2000
Hadnot Point	Hadnot Point	1943-2000
Rifle Range	Rifle Range	1941-1993
	Onslow County	1994-2000

Source: Marine Corps, personal commun., March 13, 2008.

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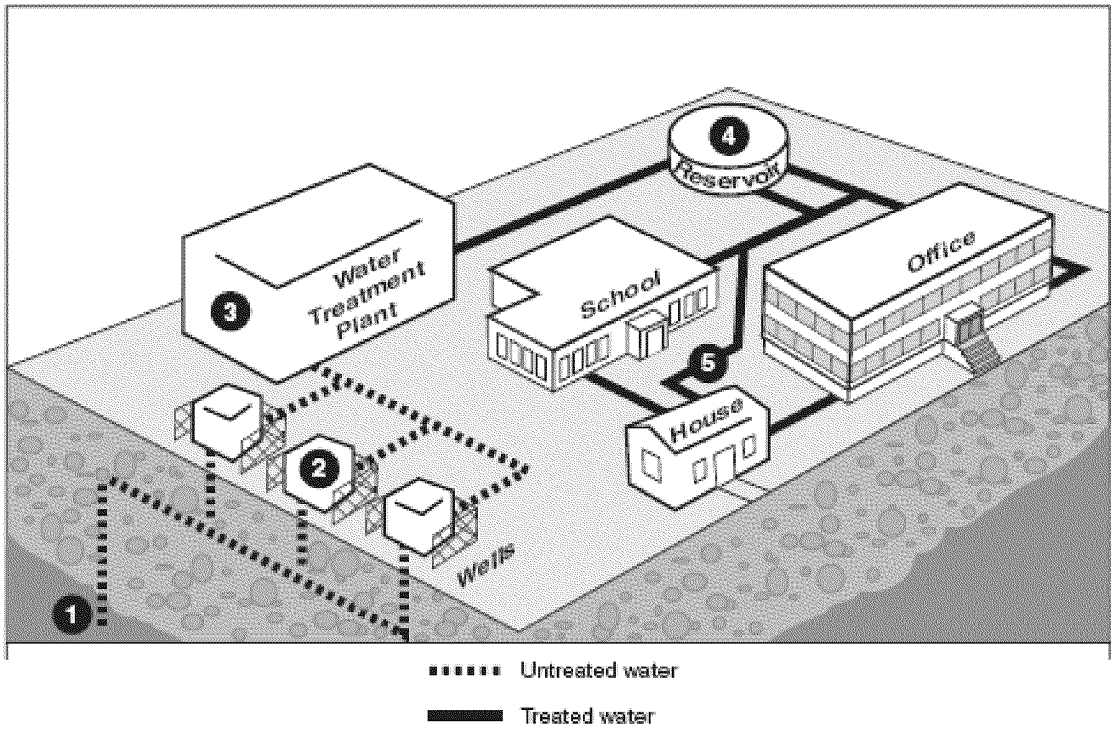


FIGURE 2-4 Conceptual model of a Camp Lejeune water system. (1) The drinking water at Camp Lejeune is obtained from groundwater pumped from a freshwater aquifer located approximately 180 ft below the ground. (2) Groundwater is pumped through wells located near the water-treatment plant. (3) In the water-treatment plant, the untreated water is mixed and treated through several processes: removal of minerals to soften the water, filtration through layers of sand and carbon to remove particles, chlorination to protect against microbial contamination, and fluoride addition to help prevent tooth decay. (4) After the water is treated, it is stored in ground and elevated storage reservoirs. (5) When needed, treated water is pumped from the reservoirs and tanks to facilities, such as offices, schools, and houses on the base. Source: GAO 2007.

Review of Contaminated Areas

The committee evaluated data on hazardous-waste site locations and characteristics in the vicinity of the water-supply well and residential service locations for the water systems listed in Table 2-1 (Baker Environmental, Inc 1999, CH2M Hill and Baker Environmental, Inc 2005). Table 2-2 summarizes the contaminants found in soil or groundwater at waste sites near supply wells. Details of the contamination near supply wells serving Tarawa Terrance and Hadnot Point are presented later in this chapter. Waste sites in the vicinity of other water-supply areas are described briefly in Appendix C (Table C-1).

COMMITTEE'S WATER-SUPPLY EVALUATION APPROACH

The committee focused its attention on the Tarawa Terrace and Hadnot Point water-supply systems. The systems were evaluated differently because much more work had been done to characterize the contamination of the Tarawa Terrace system than that of the Hadnot Point system. For Tarawa Terrace, the committee relied exclusively on reports by ATSDR (Faye 2007; Lawrence 2007; Faye and Green 2007; Faye and Valenzuela 2007; Maslia et al. 2007; Faye 2008; Jang and Aral 2008; Wang and Aral 2008). The reports included analyses of the water-quality data conducted in conjunction with ATSDR's

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TABLE 2-2 Contaminants Found in Soil or Groundwater at Hazardous Waste Sites Near Water-Supply Wells

Water System	Approximate Number Identified Hazardous-Waste Sites	Contaminants Detected in Soils (S) or Monitoring Wells (M, D)
Tarawa Terrace	2	Chlorinated solvents (S ,M, D) BTEX (S, M)
Hadnot Point	13	Pesticides (S, M) Polychlorinated biphenyls (S) Metals (S, M) Chlorinated solvents (S, M, D) Fuel compounds (M) Benzene (M) Toluene (M) Ethylbenzene (M) Xylenes (M) BTEX (M) Petroleum products (S, M) Volatile compounds (S) Semivolatile compounds (S)
Holcomb Boulevard	5	Pesticides (S, M) Volatile and semivolatile compounds (S, M) Metals (M)
Marine Corps Air Station	6	Volatile and semivolatile compounds at two locations (S, M) Pesticides at one location (S, M)
Rifle Range	2	VOCs (M)
Camp Geiger	13	Chromium (M) Lead (M) VOCs (M)
Camp Johnson	2	None

Abbreviations: BTEX = benzene, toluene, ethylene, and xylene; D = deeper wells in Castle Hayne aquifer, source of water-supply wells; M = shallow wells, surficial aquifer, or soil vadose zone.
Sources: Baker Environmental, Inc 1999; CH2M Hill and Baker Environmental, Inc 2005.

water-quality modeling. For Hadnot Point, the committee conducted its own review of information that was in the public record. The committee used multiple sources, including the 2007 GAO report, remedial investigation reports (Baker Environmental, Inc 1993, 1994, 1995), data summarized in the "Camp Lejeune water"(CLW) documents (CD accompanying Maslia et al. 2007), and planning documents from ATSDR (Maslia 2008). The goal was to get an understanding of the contamination of water supplies serving Hadnot Point residents, including which VOCs were of potential concern and the degree to which contaminant concentrations in the water supply varied. In consulting the CLW documents, the committee focused on contaminant measurements taken while the contaminated wells were operating, including measurements of the water-supply wells and from the water-treatment plant and distribution system. As noted earlier, water from the supply wells was mixed at the water-treatment plant before distribution. Because all water samples from the distribution system were taken after water from multiple supply wells was mixed, they were categorized as "mixed" water samples. Sampling of mixed water occurred before and after water was treated or "finished." Samples taken from mixed water give a better indication of the concentrations of contaminants delivered to the tap than samples taken from supply wells. However, water-quality data on the individual supply wells shed light on the wells that were contaminated and permit preliminary documentation of the extent of contamination.

In determining its approach to evaluating the water-quality data on Hadnot Point, the committee wrestled with reporting data that have not been collected by a process that involved standard quality-assurance procedures. The process that was used for abstraction of the water-quality data (see Appendix

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C) did not consider multiple aspects of the data, including the sampling strategy, methods for sample collection and analysis, chain of custody of samples, recording and interpretation of detection or quantitation limits, and duplication of sampling results in source documents. Thus, the data cited are only for illustrative purposes, and references to the primary documents are provided to facilitate additional work.

TARAWA TERRACE WATER SUPPLY

Discovery and Investigation of the Contamination at Tarawa Terrace

The Tarawa Terrace water-supply system began operations in 1952. Seven wells initially supplied water to the system, and more wells were added over the years. A total of 16 wells served the system at some time between 1952 and 1987. The wells operated on a cycled schedule. Wells were taken offline or were closed for various reasons between 1962 and 1987 (Maslia et al. 2007).

During August 1982, a routine analysis with gas chromatography-mass spectrometry (to screen the water samples collected from the Tarawa Terrace water-treatment plant for chlorination byproducts) indicated high concentrations of halogenated hydrocarbons, a class of VOCs (Faye and Green 2007). Further analysis confirmed the presence of PCE in finished water at 76-104 µg/L (Faye and Green 2007). Sporadic sampling in 1982-1985 also indicated detectable concentrations of TCE, which is a degradation byproduct of PCE.

In January 1985, the North Carolina Department of Natural Resources and Community Development (NCDNRCD) began routine sampling of water from supply wells TT-23, TT-25, and TT-26 and finished water from the water-treatment plant (Faye 2008). The data indicated varied PCE and TCE contamination. For example, PCE ranged from nondetectable to 132 µg/L and from 3.8 to 1,580 µg/L in wells TT-23 and TT-26, respectively. Wells TT-23 and TT-26 were temporarily removed from service in February 1985. Later, well TT-26 was closed permanently, and well TT-23 was used intermittently for several days during March and April 1985 and finally shut down in April 1985 (GAO 2007). From January to September 1985, samples were taken from wells TT-30, TT-31, TT-52, TT-54, and TT-67, and PCE and its degradation products were not detected.

In April 1985, NCDNRCD conducted extensive field investigation to map the PCE plume and identify the contaminant source. On the basis of that investigation, the northwest edge of the plume was determined to be close to ABC One-Hour Cleaners. A shallow monitoring well installed close to the cleaners detected an extremely high PCE concentration of 12,000 µg/L (Faye and Green 2007). Such a high concentration is an indication of a source region that contains pure-phase PCE (the highest possible concentration of PCE in water is about 110,000 µg/L). Further investigations revealed that ABC One-Hour Cleaners had routinely used PCE in dry-cleaning operations since 1953. Shiver (1985) reported that PCE releases from various accidental spills entered the septic system through a floor drain. Furthermore, spent PCE was routinely put through a filtration-distillation process that produced dry still bottoms (sludge). Until about 1982, such waste products were used to fill potholes in a nearby alleyway. The exact date of the termination of those disposal practices is unknown; ATSDR estimates that they ceased in 1985 (Faye and Green 2007).

Several on-base sources and episodes were documented. Faye and Green (2007) report that a "strong gasoline type odor" was noted at water-supply well TT-53 during October 1986 while personnel from the U.S. Geological Survey (USGS) conducted a routine well reconnaissance. The well was not in service at the time. The gasoline contamination was traced to various spills and leaks from 12 underground storage tanks (USTs) associated with various buildings in the Tarawa Terrace shopping center. For example, on September 21, 1985, a catastrophic failure discharged about 4,400 gal of unleaded gasoline to the subsurface. A review of past releases indicated that small leaks of gasoline products probably occurred at the site beginning in the 1950s. As of May 4, 1987, more than 2 ft of floating gasoline was determined to be present above the water table in the vicinity of Building TT-2453.

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Investigation of groundwater contamination due to sources other than the ABC One-Hour Cleaners began after 1990 (Faye and Green 2007). The investigations focused on above-ground petroleum-storage tanks, buildings that housed filling stations, and USTs. The above-ground tanks were between State Route 24 and the railroad tanks near water-supply wells TT-27 and TT-55. They were constructed in 1942 and stored petroleum until about 1980, when they were converted to waste-oil storage. Most of the remedial investigations of buildings and USTs focused on areas in or near the Tarawa Terrace shopping center. Information on the installation, use, and release histories of the USTs is sparse. At least some of the tanks may have been constructed as early as the 1950s. High concentrations of benzene and toluene were measured in samples taken from monitoring wells, and several benzene plumes were mapped as a result of those investigations (see Faye and Green 2007, Table E9 and Figures E7 and E9).

Other Contaminants of Concern at Tarawa Terrace

PCE is the primary contaminant at the Tarawa Terrace site, but other contaminants have been detected in supply wells, including TCE, 1,1-dichloroethylene (DCE), *cis*- and *trans*-1,2-DCE, benzene, toluene, and vinyl chloride. Many of these contaminants—including TCE, DCE, and vinyl chloride—may have resulted from degradation of PCE. Microorganisms in the subsurface degrade PCE to TCE under favorable anaerobic conditions. TCE later degrades to DCE (primarily *cis*-1,2-DCE [Bradley 2003]); similarly, DCE degrades to vinyl chloride and eventually to ethane, an innocuous degradation product (Bradley 2003; Clement et al. 2000; Clement et al. 2002). Some of the chlorinated compounds (including TCE, DCE, and vinyl chloride) can also be aerobically oxidized to yield carbon dioxide (Clement et al. 2000; Bradley 2003). At the ABC One-Hour Dry Cleaners site, water samples from monitoring wells in the waste-disposal zone contained TCE at concentrations up to 690 µg/L and total DCE at up to 1,200 µg/L on April 23, 1992 (Faye and Green 2007). The highest measured concentrations of TCE and total DCE in the Tarawa Terrace supply wells were 62 µg/L (estimated value on July 11, 1991) and 92 µg/L (measured value on January 16, 1985), respectively (Faye and Green 2007).

Water-Quality Data on the Tarawa Terrace System

ATSDR (Faye and Green 2007) lists 16 wells that served the Tarawa Terrace water-supply system. Two of them (TT-26 and TT-23 [also referred to as TT New Well]) were shut down on February 8, 1985, because of PCE contamination (GAO 2007). However, well TT-23 was used briefly after that date—at least on March 11-12, 1985, and on April 22, 23, and 29, 1985 (GAO 2007). ATSDR indicates that the well was removed from service in May 1985. Table 2-3 presents the PCE concentrations found in samples taken from various supply wells, including TT-23 and TT-26. Well TT-26 was highly contaminated. The highest concentration (1,580 µg/L) was obtained while the well was in service. Concentration decreased appreciably after the well was taken off line and then increased. Well TT-23 also showed evidence of PCE contamination. Again, the highest concentration was found after a period of regular operation in January 1985, and concentration was lower in later periods; notably, concentration was higher after 24 h of continuous operation (on March 12, 1985) than at the beginning of that period of service.

Measurements of mixed water samples suggest that supply wells TT-23 and TT-26 were major contributors to contamination of the Tarawa Terrace water supply. ATSDR (Faye and Green 2007) summarized results of analyses of PCE, TCE, and *trans*-1,2-DCE measured in water samples collected from May 1982 to October 1985 at the Tarawa Terrace water-treatment plant and locations (some unknown) throughout the water-distribution system (see Table 2-4). TCE and *trans*-1,2-DCE were not measured in all water samples (indicated by a "-" in the table). PCE ranged from undetected to 215 µg/L; the highest reported concentration was in a water sample collected from storage tank STT-39A on February 11, 1985, several days after wells TT-23 and TT-26 were removed from service. With the exception of that sample,

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TABLE 2-3 Observed Concentrations of PCE in Tarawa Terrace Water-Supply Wells

Sample Date	PCE, µg/L	Detection Limit, µg/L
Supply well TT-23		
Jan. 16, 1985	132	10
Feb. 12, 1985	37	10
Feb. 19, 1985	26.2	2
Feb. 19, 1985	ND	10
Mar. 11, 1985	14.9	10
Mar. 11, 1985	16.6	2
Mar. 12, 1985	40.6	10
Mar. 12, 1985	48.8	10
Apr. 9, 1985	ND	10
Sept. 25, 1985	4[a]	2
July 11, 1991	ND	10
Supply well TT-25		
Feb. 5, 1985	ND	10
Apr. 9, 1985	ND	10
Sept. 25, 1985	0.43[a]	10
Oct. 29, 1985	ND	10
Nov. 4, 1985	ND	10
Nov. 12, 1985	ND	10
Dec. 3, 1985	ND	10
July 11, 1991	23	10
Supply well TT-26		
July 16, 1985	1,580	10
Feb. 12, 1985	3.8	10
Feb. 19, 1985	64	10
Feb. 19, 1985	55.2	10
April 9, 1985	630	10
June 24, 1985	1,160	10
Sept. 25, 1985	1,100	10
July 11, 1991	350	10
Supply well TT-30		
Feb. 6, 1985	ND	10
Supply well TT-31		
Feb. 6, 1985	ND	10
Supply well TT-52		
Feb. 6, 1985	ND	10
Supply well TT-54		
Feb. 6, 1985	ND	10
July 11, 1991	ND	5
Supply well TT-67		
Feb. 6, 1985	ND	10
Supply well RW1		
July 12, 1991	ND	2
Supply well RW2		
July 12, 1991	760	2
Supply well RW3		
July 12, 1991	ND	2

[a]Estimated value.
Abbreviation: ND = not detected.
Source: Adapted from Maslia et al. 2007.

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TABLE 2-4 Summary of Selected Analyses for PCE, TCE, and *trans*-1,2-DCE in Water Samples Collected at Tarawa Terrace Water-Treatment Plant and Tarawa Terrace Addresses

Sample Location or *Event*	Date	PCE, µg/L	TCE, µg/L	*Trans*-1,2-DCE, µg/L	Detection Limit, µg/L
Tap water at Bldg. TT-2453	May 27, 1982	80	—	—	Unknown
Tap water at Bldg. TT-2453	July 28, 1982	104	—	—	Unknown
TTWTP Bldg. TT-38	July 28, 1982	76	—	—	Unknown
TTWTP Bldg. TT-38	July 28, 1982	82	—	—	Unknown
Tap water; address unknown	Feb. 5, 1985	80	8.1	12	Unknown
Well TT-26 shut down	Feb. 8, 1985				
Well TT-23 initially shut down[a]	Feb. 8, 1985				
TTWTP Tank STT-39	Feb. 11,1985	215	8	12	10
TTWTP Bldg. TT-38	Feb. 13, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Feb. 19, 1985	ND	ND	ND	2
TTWTP Bldg. TT-38	Feb. 22, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Mar. 11, 1985	ND[a]	ND[a]	ND[a]	2
TTWTP Bldg. TT-38	Mar. 12, 1985[b]	6.6[a]	ND[a]	ND[a]	10
TTWTP Bldg. TT-38	Mar. 12, 1985[b]	8.9[a]	ND[a]	ND[a]	2
TTWTP Bldg. TT-38	Mar. 12, 1985[c]	20[a]	1.1[a]	1.2[a]	2
TTWTP Bldg. TT-38	Mar. 12, 1985[c]	21.3[a]	ND[a]	ND[a]	10
TTWTP Bldg. TT-38	Apr. 22, 1985	1[a]	4.1[a]	ND[a]	10
TTWTP Bldg. TT-38	Apr. 23, 1985	ND[a]	1.4[a]	ND[a]	10
TTWTP Bldg. TT-38	Apr. 29, 1985	3.7[a]	ND[a]	—	10
Well TT-23 ceases to operate	May 1985				
TTWTP Bldg. TT-38	May 15, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	July 1, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	July 8, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	July 23, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	July 31, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Aug. 19, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Sept.11, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Sept. 17, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Sept. 24, 1985	ND	ND	ND	10
TTWTP Bldg. TT-38	Oct. 29, 1985	ND	ND	ND	10

[a]Intermittent operation of well TT-23 after February 8, 1985, including at least March 11 and 12 and April 22, 23, and 29, 1985.
[b]Samples collected downstream of TTWTP reservoir after well TT-23 operated for 24 h.
[c]Samples collected upstream of TTWTP reservoir after well TT-23 operated for 24 h.
Abbreviations: — = constituent not determined; ND = not detected; TTWTP = Tarawa Terrace water-treatment plant.
Source: Adapted from Table E12 of Faye and Green 2007.

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quantified samples were collected on dates when TT-23 or TT-26 was contributing to the water supply. Most of the analytic results listed in Table 2-4 had nondetectable concentrations of TCE and *trans*-1,2-DCE, but not all samples were tested for these chemicals. Before February 8, 1985, those compounds were measured in only one water sample, which contained TCE at 8.1 µg/L and *trans*-1,2-DCE at 12 µg/L. Similar concentrations of TCE and *trans*-1,2-DCE (8 and 12 µg/L, respectively) were reported in the water-storage tank sample (STT-39A, February 11, 1985).

Faye and Green (2007) also summarized analytic results for benzene and toluene in finished-water samples collected at the Tarawa Terrace water-treatment plant in 1985 (see Table 2-5). Benzene reportedly ranged from "not detected" to 2 µg/L and toluene from "not detected" to 4 µg/L; all concentrations were below the stated laboratory detection limit of 10 µg/L. (The accuracy of values below the detection limit is less certain.) It is notable that all samples in which benzene and toluene were detected were taken after February 8, 1985, the date when the two contaminated wells were closed, except for one sample with detection of benzene taken on March 11, 1985, during a period in which well TT-23 was temporarily back in service). The low concentrations (below the detection limit) of benzene and toluene in finished water and high measurements at a few monitoring wells (Faye and Green 2007) suggest that TT-23 and TT-26 may not have been the only source of VOC contamination in the Tarawa Terrace water-supply system. Analytic results on samples collected in 1986 from the Tarawa Terrace water-treatment plant are available (for example, on a CD accompanying Maslia et al. 2007) but have yet to be summarized.

Groundwater Fate and Transport Modeling

ATSDR performed a historical reconstruction and analysis of the contamination of the Tarawa Terrace water-supply system. It involved analyses of groundwater flow, contaminant fate and transport (of PCE and its decay products; benzene and other petroleum contaminants were not considered), and distribution in the water system. This section provides a brief review of the groundwater-modeling efforts reported in a series of ATSDR reports, including Chapters A, B, C, D, E, F, G, and H, that were made available to the committee (Faye 2007; Faye and Green 2007; Faye and Valenzuela 2007; Lawrence 2007; Maslia et al. 2007; Faye 2008; Jang and Aral 2008; Wang and Aral 2008).

Description of ATSDR's Modeling Efforts for Tarawa Terrace

ATSDR personnel used the USGS model MODFLOW to simulate groundwater flow at the site (Faye and Valenzuela 2007) and the U.S. Environmental Protection Agency (EPA) model MT3DMS to simulate PCE transport (Faye 2008). MODFLOW is a three-dimensional finite-difference code that is capable of simulating groundwater head distribution under both steady-state and transient-flow conditions. MT3DMS is a three-dimensional transport model that is directly coupled to MODFLOW. MODFLOW and other MODFLOW-family transport codes are well-established public-domain codes that are routinely used in court cases to simulate the fate and transport of dissolved chemicals (Denton and Sklash 2006); however, they invoke several assumptions for simulating complex DNAPL contaminants, such as PCE. For example, MT3DMS can predict the transport only of dissolved contaminants, so a key approximation was made to represent the mass dissolved from the DNAPL source. To apply MT3DMS, ATSDR replaced the highly complex DNAPL contaminated source zone with a hypothetical model node where PCE was injected directly into the saturated aquifer formation at a constant rate (1.2 kg/day).

ATSDR in collaboration with personnel from the Georgia Institute of Technology also used a groundwater simulation and optimization tool, the Pumping Schedule Optimization System (PSOpS), to evaluate the effect of pumping-schedule variations on PCE arrival at water-supply wells (Wang and Aral

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TABLE 2-5 Benzene and Toluene Concentrations in Water Samples Collected at Tarawa Terrace Water-Treatment Plant[a]

Site Name	Date	Benzene, µg/L	Toluene, µg/L
TTWTP Bldg. TT-38	Feb. 13, 1985	ND	ND
	Feb. 22, 1985	ND	ND
	Mar. 11, 1985	1.6	—
	Apr. 22, 1985	ND	ND
	Apr. 23, 1985	ND	ND
	May 15, 1985	ND	ND
	July 1, 1985	ND	ND
	July 8, 1985	ND	ND
	July 23, 1985	ND	ND
	July 31, 1985	ND	ND
	Aug. 19, 1985	ND	ND
	Sept. 11, 1985	ND	4
	Sept. 17, 1985	ND	ND
	Sept. 24, 1985	ND	ND
	Oct. 29, 1985	ND	ND
	Dec. 2, 1985	2	—
	Dec. 18, 1985	1	—
TTWTP tank SST-39A	Feb. 11, 1985	ND	ND

[a]Detection limit for all analyses was 10 µg/L.
Abbreviations: — = constituent not determined; ND = not detected; TTWTP = Tarawa Terrace water-treatment plant.
Source: Faye and Green 2007.

2008). In addition, the team used a multiphase transport simulator, TechFlowMP, which has the capability to use first-order biodegradation kinetics to simulate the fate and transport of PCE and its byproducts TCE, DCE, and vinyl chloride (Jang and Aral 2008). Unlike the MODFLOW and MT3DMS codes, the PSOpS and TechFlowMP codes lack validation by a broad spectrum of practicing geoscientists in an open-source environment.

ATSDR combined the hydrostratigraphic units above the Castle Hayne aquifer and modeled them as a single unconfined layer. The modelers assumed this layer to be underlain by a local confining layer. The permeable Castle Hayne aquifer formation, where all the water-supply wells are, is assumed to be below that confining layer. In the model, the Castle Hayne aquifer formation is divided into five distinct units. The details of all the modeled hydrogeologic units, their assumed thicknesses, and the corresponding model layer numbers that represent the units are summarized in Table 2-6. In both MODFLOW and MT3DMS, the subsurface was conceptualized as a fully saturated flow environment with seven layers that represented various hydrogeologic conditions. The model parameters used in the flow and transport models are summarized in Table 2-7. The boundary conditions of the models included generalized head boundary in the northern and northeastern edges of the model, no flow boundary in the western edge (which followed a natural divide), and constant head boundary conditions in the southern edge and part of the southeast direction. On the basis of rainfall data, an average recharge to the aquifer was estimated to be 13.2 in/year. The DNAPL source zone was represented by using a model node where PCE was injected continuously into the unconfined model layer-1 of the saturated zone at a constant rate of 1.2 kg/day (Faye 2008).

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TABLE 2-6 Assumed Thickness and Layer of Castle Hayne Aquifer Units

Geologic Unit	Thickness, ft	Layer No.
Tarawa Terrace unit (surficial layer)	8-30	1
Tarawa Terrace confining unit (surficial layer)	8-20	1
Upper Castle Hayne aquifer-River Bend unit (surficial layer)	16-56	1
Local confining unit	7-17	2
Upper Castle Hayne aquifer-lower unit	8-30	3
Middle Castle Hayne aquifer confining unit	12-28	4
Middle Castle Hayne aquifer	32-90	5
Lower Castle Hayne aquifer confining unit	18-30	6
Lower Castle Hayne aquifer	41-64	7
Beaufort confining layer	Bottom boundary	N/A

Source: Modified from Faye and Valenzuela 2007.

ATSDR calibrated the MODFLOW and MT3DMS models for Tarawa Terrace by using a "hierarchical process" that included the simulation of the following four successive scenarios: (1) predevelopment (before the 1950s) flow conditions without pumping, (2) transient flow conditions involving pumping, (3) fate and transport of the PCE plume, and (4) concentration of PCE at the Tarawa Terrace water-treatment plant and water-distribution system. The first two steps involved flow modeling exclusively, and the latter two steps involved combined modeling of groundwater flow and PCE transport. The groundwater-flow patterns and PCE concentration contours predicated for the surficial layer (model layer 1) for December 1984 is shown in Figure 2-5. The results of the PCE modeling study with MT3DMS indicated that the vast majority of the PCE that reached Tarawa Terrace water-treatment plant came from well TT-26. The model results show that PCE at well TT-26 exceeded EPA's current maximum contaminant level (MCL) for drinking water of 5 µg/L as early as January 1957 and that a corresponding breakthrough of PCE in well TT-23 occurred roughly in December 1974 (Faye 2008). The model-predicted groundwater concentrations and the simulated extraction rates were used in a mixing model to evaluate the flow-weighted PCE concentration at the water-treatment plant. Those estimates indicated that the concentration of PCE in the water-treatment plant output exceeded the MCL during October or November 1957 and that the concentrations remained above the MCL until the termination of pumping at well TT-26 in 1985. On the basis of ATSDR's model results, the estimated maximum concentration of PCE at the Tarawa Terrace water-treatment plant was 183 µg/L in March 1984. In the period November 1957-February 1987, the average concentration of PCE at the plant was 70 µg/L.

The estimated PCE concentration range should, however, be interpreted with considerable caution because comparison of the model predictions with measured data at various locations, as summarized in Table 2-8 and by Faye (2008), shows that the model predictions systematically overpredicted the point measurements in samples from supply wells TT-23 and TT-25. Also, the model results show a monotonically increasing trend, whereas the measured data are highly random. It is important to note that comparison of monthly averaged model predictions with point measurements from various locations is problematic, although this practice is not uncommon in calibration of groundwater models like this application by ATSDR (Faye 2008). Clearly, the model predictions are influenced by temporal and spatial averaging effects. In the model, the temporal variations in pumping stresses are averaged over a month, and the temporal variations in the DNAPL source release rate are averaged over a year, whereas the data on the wells' water quality represent a single time and are relevant on a much shorter time scale—hours instead of months. Similarly, spatial variations in concentration are averaged over a relatively large control volume represented by the model grid cells (the typical volume of a computational cell in layer 1 is about 100,000 ft^3), whereas the water-quality data represent spatial variations on the scale of the control volume represented by the well (estimated at about 10-1,000 ft^3).

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TABLE 2-7 Calibrated Model Parameter Concentrations Used to Simulate Groundwater Flow and Contaminant Fate and Transport in Tarawa Terrace and Vicinity

Model Parameter[a]	Model Layer[b]						
	1	2	3	4	5	6	7
Predevelopment groundwater-flow model (conditions before 1951)							
Horizontal hydraulic conductivity, K_H (ft/day)	12.2-53.4	1.0	4.3-20.0	1.0	6.4-9.0	1.0	5.0
Ratio of vertical to horizontal hydraulic conductivity, K_V/K_H[c]	1:7.3	1:10	1:8.3	1:10	1:10	1:10	1:10
Infiltration (recharge), I_R (in./year)	13.2	—	—	—	—	—	—
Transient groundwater-flow model(January 1951–December 1994)							
Specific yield, S_y	0.05	—	—	—	—	—	—
Storage coefficient, S	—	4.0×10^{-4}	4.0×10^{-4}	4.0×10^{-4}	4.0×10^{-4}	4.0×10^{-4}	4.0×10^{-4}
Infiltration (recharge), I_R (in./year)	6.6-19.3	—	—	—	—	—	—
Pumpage, Q_k (ft^3/day)	[d]	—	[d]	—	0	—	0
Fate and transport of PCE model (January 1951–December 1994)							
Distribution coefficient, K_d (ft^3/g)	5.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}
Bulk density, ρ_b (g/ft^3)	77,112	77,112	77,112	77,112	77,112	77,112	77,112
Effective porosity, n_E	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Reaction rate, r (d^{-1})	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}
Mass-loading rate[e], $q_S C_S$ (g/day)	1,200	—	—	—	—	—	—
Longitudinal dispersivity, α_L (ft)	25	25	25	25	25	25	25
Traverse dispersivity, α_T (ft)	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Vertical dispersivity, α_V (ft)	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Molecular-diffusion coefficient, D* (ft^2/day)	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}

[a]Symbolic notation used to describe model parameters obtained from Chiang and Kinzelbach (2001).
[b]Refer to Chapter B (Faye 2007) and Chapter C (Faye and Valenzuela 2007) reports for geohydrologic framework corresponding to appropriate model layers; aquifers are model layers 1, 3, 5, and 7; confining units are model layers 2, 4, and 6.
[c]For model cells simulating water-supply wells, vertical hydraulic conductivity (K_v) equals 100 ft/day to approximate gravel pack around well.
[d]Pumpage varies by month, year, and model layer; refer to Chapter K report (Maslia et al. in press) for specific pumpage data.
[e]Introduction of contaminant mass began in January 1953 and ended in December 1984.
Abbreviations: — = not applicable; d^{-1} = 1/day.
Source: Maslia et al. 2007.

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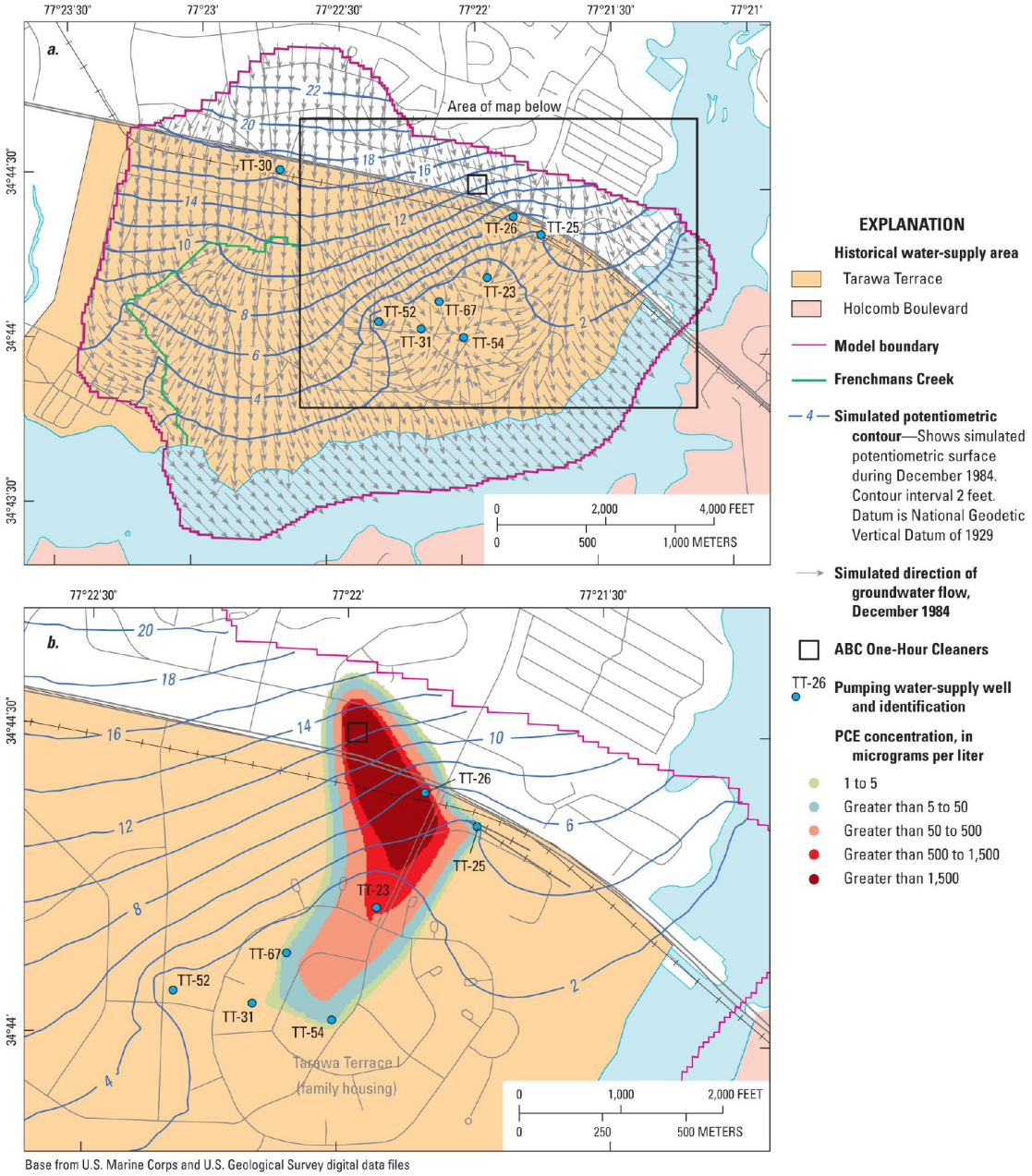


FIGURE 2-5 Simulated (*a*) water level and direction of groundwater flow, and (*b*) distribution of tetrachloroethylene (PCE), model layer 1, December 1984, Tarawa Terrace and vicinity, U.S. Marine Corps Base Camp Lejeune, North Carolina. Source: Maslia et al. 2007.

The modeling studies did not include any formal analysis to account for the temporal or spatial data-averaging effects. Instead, in the analysis presented by Faye (2008), the point measurements were used to set a "calibration target range" for constraining the model predictions; the range was arbitrarily set at about half the order of magnitude of the detected point measurements (Faye 2008); the actual target ranges used are shown in Table 2-8. For concentrations that are reported as nondetected, the lower target was set to 1 µg/L, and the upper limit was set at the analytic detection limit (Faye 2008).

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TABLE 2-8 Simulated and Observed PCE Concentrations at Water-Supply Wells and Calibration Target Range, Tarawa Terrace and Vicinity

Site	Date	PCE Concentration, µg/L		Calibrated Target Range, µg/L
		Observed	Simulated	
RW1	July 12, 1991	ND	0.0	0.0-2.0
RW2	July 12, 1991	760	1,804	240-2,403
RW3	July 12, 1991	ND	0.0	0.0-2.0
TT-23	Jan. 16, 1985	132	254	41.7-417
	Feb. 12, 1985	37.0	254	11.7-117
	Feb. 19, 1985	26.2	253	8.3-82.8
	Feb. 19, 1985	ND	253	0.0-10.0
	Mar. 11, 1985	14.9	253	4.7-47.1
	Mar. 11, 1985	16.0	253	5.2-52.5
	Mar. 12, 1985	40.6	253	12.8-128
	Mar. 12, 1985	48.0	253	15.4-154
	Apr. 9, 1985	ND	265	0.0-2.0
	Sept. 25, 1985	4.0	279	0.3-12.6
	July 11, 1991	ND	193	0.0-5.0
TT-25	Feb. 5, 1985	ND	6.2	0.0-10.0
	Apr. 9, 1985	ND	8.6	0.0-2.0
	Sept. 25, 1985	0.43[a]	18.1	0.14-1.4
	Oct. 29, 1985	ND	20.4	0.0-10.0
	Nov. 4, 1985	ND	20.4	0.0-10.0
	Nov. 13, 1985	ND	20.4	0.0-10.0
	Dec. 3, 1985	ND	22.8	0.0-10.0
	July 11, 1991	23.0	72.6	7.3-72.7
TT-26	Jan. 16, 1985	1,580	804	500-5,000
	Feb. 12, 1985	3.8	804	1.2-12
	Feb. 19, 1985	55.2	798	17.5-175
	Feb. 19, 1985	64.0	798	20.2-202
	Apr. 9, 1985	630	801	199-1,999
	June 24, 1985	1,160	732	367-3,668
	Sept. 25, 1985	1,100	788	348-3,478
	July 11, 1991	340	670	111-1,107
TT-30	Feb. 6, 1985	ND	0.0	0.0-10.0
TT-31	Feb. 6, 1985	ND	0.15	0.0-10.0
TT-52	Feb. 6, 1985	ND	0.0	0.0-10.0
TT-54	Feb. 6, 1985	ND	5.8	0.0-10.0
	July 11, 1991	ND	30.4	0.0-5.0
TT-67	Feb. 6, 1985	ND	3.9	0.0-10.0

[a]Estimated.
Abbreviation: ND = not detected.
Source: Faye 2008.

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ATSDR stated concerns about uncertainties in the pumping-schedule data used in the PCE modeling study discussed above and in the date when the MCL was predicted to be exceeded in water-supply wells and at the water-treatment plant (Faye 2008). ATSDR assumed that the major cause of uncertainty in the models was associated with pumping schedules. To address that issue, ATSDR applied PSOpS to evaluate the effect of variation in pumping schedules on the prediction of when the concentration of PCE would exceed EPA's MCL of 5.0 µg/L (Wang and Aral 2008). Analysis of PSOpS results indicated that the change in pumping schedules would change the date when the MCL was exceeded in well TT-26 from May 1956 to August 1959 and at the water-treatment plant from December 1956 to June 1960. Because insufficient historical pumping data were available to constrain the model predictions from 1953 to 1980, the ability of the advanced optimization models to estimate the dates accurately is questionable.

Biodegradation is one of the major processes by which PCE can be removed from groundwater. Under favorable natural conditions, PCE can degrade to toxic substances. ATSDR used the multiphase research tool TechFlowMP to simulate the fate and transport of PCE with three decay products: TCE, *trans*-1,2-DCE, and vinyl chloride (Jang and Aral 2008). The TechFlowMP model also predicted PCE vapor concentrations. PCE biodegradation is mediated by a series of coupled reactive transport processes, primarily under highly anaerobic conditions (Bradley 2003), and little is understood about the underlying biodegradation mechanisms. There are several controversies about the types of subsurface microorganisms that could facilitate the decay reactions (Major et al. 2003; Nyer et al. 2003). Although it is not stated explicitly in the modeling reports, ATSDR made the following assumptions for the TechFlowMP simulations: (1) the entire aquifer is anaerobic (the only known biochemical condition in which PCE can degrade); (2) the aquifer has the necessary microorganisms, which are uniformly distributed; (3) the aquifer has a carbon source sufficient to support microbial growth; (4) *trans*-1,2-DCE is the only DCE species in the decay chain; and (5) there is no spatial variation in the microbiologic or geochemical characteristics. ATSDR indirectly invoked all those conditions by assuming, for example, a constant, first-order PCE biotransformation rate coefficient of 0.0005 day^{-1} for all the layers in the aquifer. It is highly unlikely that that assumed biodegradation rate is applicable to the entire site. There are no microbiologic or geologic data are available to support the five assumptions. Therefore, the predicted concentrations of TCE, *trans*-1,2-DCE, and vinyl chloride in the Castle Haynes aquifer at the location of intake by Tarawa Terrace supply wells should be used with considerable caution.

Gaps in and Limitations of the Modeling

The committee reviewed the Tarawa Terrace modeling reports and found that ATSDR applied the public-domain codes for MODFLOW and MT3DMS and two cutting-edge research codes PsOps and TechFlowMP to model the complex groundwater-contamination scenario at Tarawa Terrace. However, there are some important limitations in ATSDR's modeling efforts because of the sparse set of water-quality measurements, the need to make unverifiable assumptions, and the complex nature of the PCE source contamination. The major gaps and limitations that the committee found with regard to the historical reconstruction and modeling work are summarized below. Future modeling efforts for the Hadnot Point water system should be designed in light of these limitations.

- The effects of the DNAPL in both unsaturated and saturated zones have not been included in the studies. As constructed, the DNAPL zone has no influence in any of the Tarawa Terrace groundwater models, because for each model ATSDR assumed that PCE was injected directly at a constant rate of 1.2 kg/day (that is, multiphase flow and dissolution reactions associated with DNAPL transport were ignored). PCE dissolution is a highly heterogeneous, rate-limited, mass-transfer process (Miller et al. 1990; Jackson 1998; Abriola 2005). Hence, the constant-mass injection approach used to model the complex PCE source zone may be prone to high uncertainty. Field data or other supporting evidence would be needed to justify the mass release rates. For example, Guilbeault et al. (2005) proposed some methods to characterize DNAPL source zones to estimate mass and contaminant release rates.

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- Constant values of dispersivity (longitudinal dispersivity of 25 ft and transverse 2.5 ft) were used in the transport model. There is insufficient information available on the nature and amount of heterogeneity to use these fixed values with a sufficient level of confidence in predictive simulations.
- The basis used for setting the values of the "calibration target range" was unclear. The repeated samples collected at some of the wells (multiple samples in 1 year) may provide some important information about the variability of observations caused by subsurface variations and possibly pumping variations. Perhaps these data could be used to determine observation variability that the computer model was not constructed to reproduce.
- The numerical codes TechFLowMP and PSOpS used in the modeling are research tools and are not widely accepted public-domain codes, such as MODFLOW and MT3DMS, so their validation is important. If data are not available, the results should be used with caution and should include appropriate uncertainty estimates.
- The PSOpS modeling study is based on the premise that an optimization model can be used to evaluate pumping stresses. Without site-specific pumping and water-quality data, the results will be non-unique and uncertain.
- Review of water-quality monitoring data indicates substantial temporal variability even at a single well. For example, the seven measurements taken on well TT-26 from January to September 1985 indicates that the concentrations at this well varied from 3.8 to 1,580 µg/L (see Table 2-8). The model predictions for the same timeframe ranged from 732 to 804 µg/L. The difference indicates that the real system is highly transient and that the model did not account for temporal and spatial averaging effects.
- The TechFlowMP model predicted very high vapor concentrations. For example, TechFlowMP predicted that the PCE vapor concentration in the top 10 ft of soil beneath the Tarawa Terrace elementary school should be 137 µg/L. Studies of PCE vapor concentrations in buildings that house or are near a dry-cleaning facility have reported measured concentrations around 55 µg/L (McDermott et al. 2005). The PCE vapor concentrations predicted by TechFlowMP should be treated with caution because they are theoretical estimates that have not been validated against field data from Camp Lejeune or compared with any measured vapor concentrations at other similar dry-cleaner sites.
- The biodegradation model used within the TechFlowMP code is based on an untested preliminary research model. Biodegradation of chlorinated solvent compounds will be influenced by several types of complex biogeochemical processes. The simple first-order modeling framework that also used a single decay coefficient for the entire modeling domain may not capture those biologic complexities. Therefore, the predicted concentrations of TCE, DCE, and vinyl chloride should be considered "crude" estimates, at best, unless validated with field measurements. In addition, biodegradation-model predictions are not supported by field data on biogeochemical indicators, which are commonly used to assess whether the assumed biodegradation pathways are active at a field site (EPA 1998a).
- The TechFlowMP simulations assumed that the biodegradation byproduct of TCE is *trans*-1,2-DCE. However, the scientific literature indicates that *cis*-1,2-DCE is the predominant product of TCE reduction under in situ groundwater conditions (Bradley 2003).
- Reporting absolute predicted concentrations of PCE and its biodegradation byproducts in finished water delivered by the Tarawa Terrace water-supply system with a precision up to five significant figures without any error bounds (for example, Jang and Aral [2008] report concentrations of PCE at 102.10 µg/L, TCE at 4.33 µg/L, DCE at 13.75 µg/L, and vinyl chloride at 7.50 µg/L) provides an unwarranted sense of certainty. Such reporting can contribute to misperceptions by the public and the epidemiology-research community that water-modeling efforts can produce a specific value for contaminant concentration. Posting such precise point estimates for PCE, TCE, DCE, and vinyl chloride concentrations on public Web pages (www.atsdr.cdc.gov/sites/lejeune) and encouraging former Camp Lejeune marines and their families to find the estimated exposure concentrations of these contaminants leads to a misleading perception that reactive transport models can make accurate predictions.
- In the absence of data, historical reconstruction efforts that use groundwater models can only provide a general conceptual framework for what happened at the site and why. At best, such models may

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be used only to estimate a range of possible concentrations. Without historical geochemical data, the uncertainly associated with many of the input parameters (such as the biodegradation parameters) could be very high. In addition, current understanding of subsurface reactive transport processes is inadequate, so transport models cannot be expected to provide definitive concentration estimates especially for biodegradation byproducts.

- The inherent and, in this case, profound limitations of historical modeling due to uncertainties in various model parameters and pumping stresses should be communicated along with modeling predictions.

ATSDR has completed a detailed groundwater-modeling study and have used the best possible techniques and tools. Several of the gaps and limitations mentioned above are due to the difficulty of reconstructing accurate groundwater-contamination scenarios. Without historical data, the natural processes that occurred several decades ago simply cannot be reconstructed. The committee understands this limitation and acknowledges that ATSDR has done its best under these difficult circumstances.

HADNOT POINT WATER SUPPLY

Approximately 100 wells have supplied water to the Hadnot Point system since it began operations in 1943, although not all were operational at the same time. ATSDR is currently determining the history of the individual well operations and capacities. Like the Tarawa Terrace system, water from the supply wells was pumped to the water-treatment plant and mixed and processed before distribution on the base. In July 1972, the Holcomb Boulevard water system took over supplying water to some areas originally served by the Hadnot Point system. The two systems were connected, such that on several occasions the Hadnot Point system temporarily served or supplemented the Holcomb Boulevard system. Specifically, water from the Hadnot Point system was used periodically during summer months and for 2 weeks in 1985 when the Holcomb Boulevard system was shutdown because of an emergency.

A comprehensive water-modeling analysis has not yet been conducted for Hadnot Point, so the committee sought to identify documents that provided some quantitative information on the contamination of the Hadnot Point water-distribution system. Relevant information was found in a 2007 GAO report, documents cited by ATSDR in its evaluation of Tarawa Terrace, remedial-investigation reports, and documents provided to the committee by the public. The selection of documents reviewed was not comprehensive but was informed by discussion with the Marine Corps, ATSDR, and the public. Primary sources of information for the committee's review included contaminant measurements taken while the contaminated wells were operating and data collected from monitoring wells, which were installed to conduct testing and monitoring for remediation purposes after the supply wells were closed.

The remedial investigations and the 2007 GAO report identify TCE and PCE as the primary contaminants of concern at Hadnot Point. After reviewing additional preliminary information, the committee decided also to investigate eight other contaminants: *trans*-1,2-DCE, *cis*-1,2-DCE, 1,1-DCE, 1,1,1-trichloroethane (TCA), vinyl chloride, methylene chloride, benzene, and toluene. The most useful information on those contaminants was a set of CLW documents, available on the CD accompanying Maslia et al. (2007). The set has 1,110 files made up of over 8,700 pages of material and includes laboratory reports, memorandums, field notes, and other written documents. The CLW documents were not organized or cataloged, so it was not possible to search readily for documents that contained water-quality measurements. The committee asked the Marine Corps for guidance on which CLW documents contained water-sample values from any location on the base during 1980-1986 (see Appendix C, Table C-2, for the list provided by the Marine Corps). The committee abstracted data from the subset of CLW documents that contained water-quality results from Hadnot Point potable-well and mixed water samples before March 1985.

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It was beyond the scope of the committee's task to conduct an exposure assessment or even a full-scale data abstraction for Hadnot Point. Such an undertaking would have required a systematic review of standard laboratory practices for the sampling and analytic methods for collecting, analyzing, and reporting on water samples at the contributing laboratories during the 1980s; review of the source documents for quality assurance; information on detection and quantitation limits; identification and elimination of duplicate measurements recorded in multiple documents; and information on sampling location and conditions. The committee's review of the available documents presented below constitutes an illustration of the information that is available and should help to inform future efforts for evaluating contamination of water supplies at Hadnot Point.

Potential Sources of Contamination of Hadnot Point Water Supply

Descriptions of the sources of contamination and results of sampling of monitoring wells were obtained from remedial-investigation reports (Baker Environmental, Inc 1993, 1994, 1999). The reports summarize results of analyses of samples of groundwater collected during the late 1980s and early 1990s, after the contaminated wells supplying the Hadnot Point water-distribution system were closed. They also provide information on the timing and characteristics of waste-disposal practices that resulted in contamination of environmental media in the vicinity of water-supply wells. Those locations eventually required official remedial action under U.S. environmental laws, a process that continues today. In general, the water samples from the monitoring wells were analyzed for the presence of a suite of contaminants (EPA priority pollutants) and yielded insight into the fate and transport of the contaminants from the source to the groundwater. The committee used data from the remedial-investigation reports to gain a better understanding of the nature and extent of contamination and to refine the list of contaminants of concern.

The Navy initially identified 13 sites as potential sources of contaminants of the Castle Hayne aquifer in the Hadnot Point area (Baker Environmental, Inc 1999). Each site was assigned a number (installation restoration [IR] site number), and they were grouped into operable units (OUs) to facilitate investigation and data management. Most of the sites were active in the 1940s to 1970s, before implementation of more rigorous requirements governing waste tracking, handling, and disposal. The contaminants detected in soil or groundwater samples in the course of remedial investigations are summarized in Table 2-9. Figure 2-6 is a map of the sites in relation to housing areas and water-supply wells in the Hadnot Point area.

IR site 78, the Hadnot Point industrial area, has been a center of industrial activities since the 1940s. The site included as many as 75 buildings that housed such operations as maintenance shops, refueling stations, administrative offices, printing shops, warehouses, painting shops, storage yards, a steam-generation plant, and other light industry (Baker Environmental, Inc 1994, 1999). The remedial investigation for site 78 was preceded by several investigations that confirmed the presence of VOCs related to fuels and solvents in the groundwater. Those investigations were followed by ones that set the stage for the systematic sampling conducted for the remedial investigation in 1992.

Sites 6 and 82 were used for open storage beginning in the 1940s. Many types of materials were stored on site, including pesticides and polychlorinated biphenyls. Groundwater in the vicinity of sites 6 and 82 was sampled as part of the Confirmation Study (1984-1988). Chlorinated solvents were detected in shallow and deep (Castle Hayne aquifer) monitoring wells during the remedial investigation study (Baker Environmental, Inc 1993).

OU 7 comprises sites 1, 28, and 30. The French Creek liquids disposal area (site 1) is 1 mile southeast of the Hadnot Point industrial area and was used by mechanized artillery units starting in the 1940s to dispose of waste petroleum, oil, and lubricants by ground spreading (dumping). Sporadic contamination of the upper aquifer with TCE and vinyl chloride was documented during the remedial investigation process (Baker Environmental, Inc 1995).

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TABLE 2-9 Installation Restoration Sites in the Hadnot Point Water-Supply Area

OU and IR Site	Site Description	Contaminants Identified During Remedial Investigation
OU 1, site 21	Transformer storage lot	Soil contaminated with pesticides, polychlorinated biphenyls
OU 1, site 24	Industrial area fly ash dump	Soil contaminated with metals, pesticides; shallow groundwater contaminated with pesticides
OU 1, site 78	Hadnot Point industrial area	Groundwater (shallow and deep) contaminated with chlorinated solvents, fuel compounds (benzene, toluene, ethylbenzene, xylenes) Soils contaminated with pesticides, metals
OU 2, site 6	Storage lots 201, 203; connected to site 82	Soil contaminated with pesticides, petroleum products, metals Groundwater (shallow and deep) contaminated with chlorinated solvents
OU 2, site 9	Firefighting training pit at Piney Green Road	Low concentrations of chlorinated solvents in shallow groundwater
OU 2, site 82	Piney Green Road VOC area; connected to site 6	Groundwater (shallow and deep) contaminated with chlorinated solvents
OU 7, site 1	French Creek liquids disposal area	Shallow groundwater contaminated with petroleum products, chlorinated solvents
OU 7, site 28	Hadnot Point burn dump	Surface soils contaminated with volatile, semivolatile compounds Shallow groundwater contaminated with metals
OU 7, site 30	Sneads Ferry Road fuel tank sludge area	Soil contaminated with VOCs
OU 15, site 88	Building 25, base dry cleaners	Soil, shallow groundwater contaminated with solvents
OU 18, site 94	Former PCX service station	Groundwater contaminated with petroleum hydrocarbons, chlorinated solvents
Pre-RI 10	Original base dump	No significant contamination of soil or groundwater identified
Pre-RI 12	Explosive ordnance disposal area	No significant contamination of soil or groundwater identified

Abbreviation: RI = remedial investigation.

Site 28 is a former 23-acre burn dump, operated from 1946 to 1971, south of the Hadnot Point industrial area (Baker Environmental, Inc 1995). Solid waste from industrial operations—including construction debris, industrial waste, trash, and oil-based paint—was burned on site (Baker Environmental, Inc 1995). The remedial investigation found frequent detection of semivolatile and inorganic compounds and sporadic detection of VOCs in soil samples (Baker Environmental, Inc 1995). Shallow aquifer samples from the same period revealed the presence of lead, which was detected sporadically in the deeper water (Baker Environmental, Inc 1995).

Site 30, the Snead's Ferry Road fuel-tank sludge area, was used by contractors to clean out fuel-storage tanks. A small amount of solvents was detected in soil samples collected in 1994, but there was no indication of groundwater contamination in samples from monitoring wells (Baker Environmental, Inc 1995).

Site 88 is the location of the former on-base dry cleaners. Underground storage tanks that were installed in the 1940s, which contained Varsol (a type of mineral spirits) and PCE, were removed in 1996. In 2005, it was determined that groundwater contamination extended 50 ft below ground surface, and the resulting plume of contaminants in the groundwater extended about 500 ft to the northwest. DNAPL was present in the groundwater, but aggressive treatment has reduced concentrations (CH2M Hill and Baker Environmental, Inc 2005).

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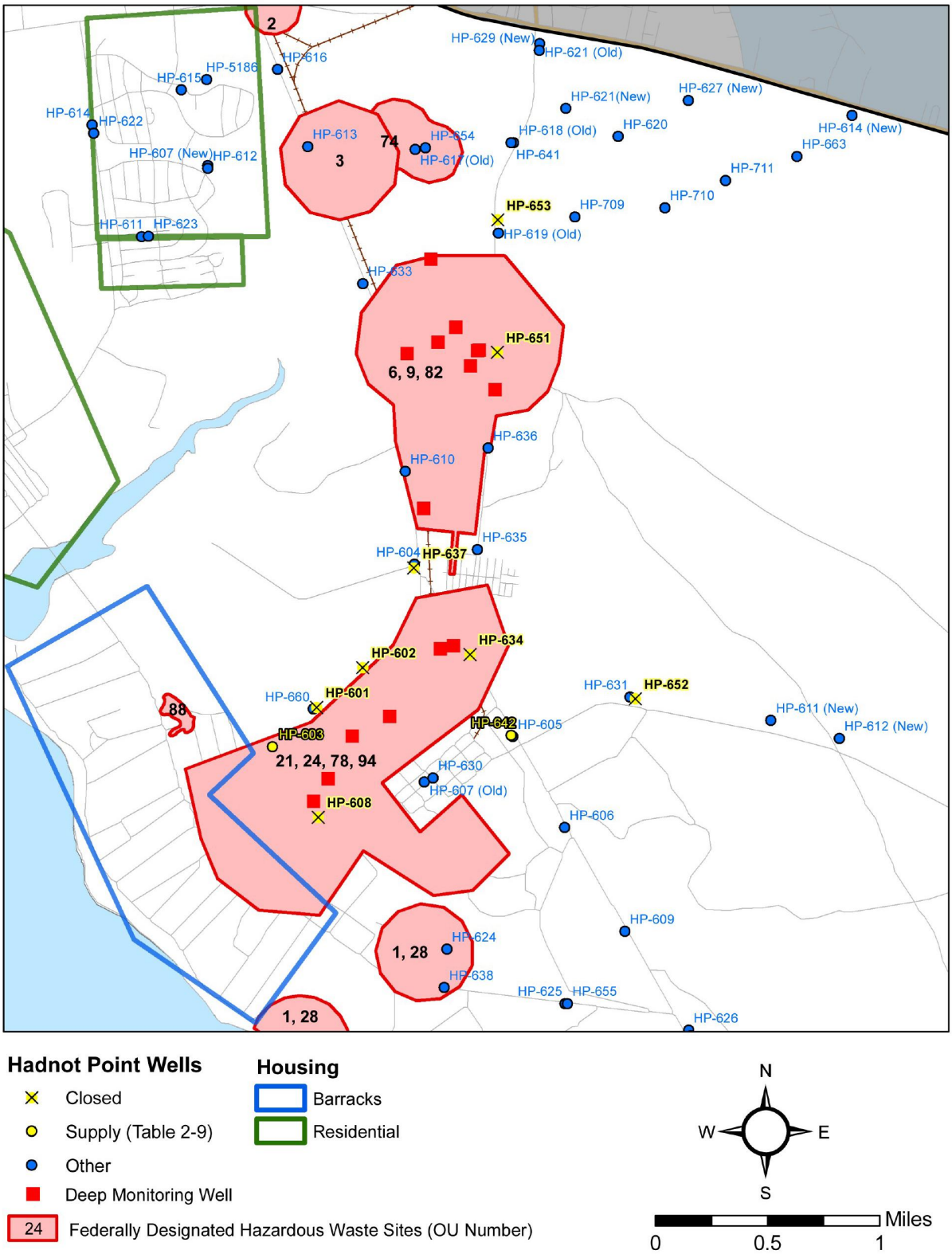


FIGURE 2-6 Designated hazardous-waste remedial investigation sites at Hadnot Point.

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Preremedial investigation (pre-RI) site 10, which was initially identified before the institution of the remedial investigation process, was the location of the original disposal area for Camp Lejeune waste. An investigation of the site in 1998 showed low concentrations of numerous organic and inorganic contaminants in the soil and in surface water and sediment from small ponds on site. Aluminum, arsenic, chromium, nickel, lead, and vanadium were detected at high concentrations in shallow groundwater samples (Baker Environmental, Inc 1999, 2001).

Pre-RI site 12 is a 10-acre former explosive-ordnance disposal area. No substantial residual contamination was detected during the remedial investigation process (Baker Environmental, Inc 1999, 2001).

Water-Quality Data on the Hadnot Point System

Published water-sampling data on Hadnot Point are sparse. One source (GAO 2007) reported on concentrations of contaminants detected in the Hadnot Point water-supply wells before they were removed from service in 1984 and 1985 (see Table 2-10). The highest concentrations of contaminants were reported for well 651, with TCE at 3,200 µg/L, PCE at 386 µg/L, and *trans*-1,2-DCE at 3,400 µg/L. The committee was also made aware of a water sample not included in the 2007 GAO report that was taken from well 651 on the day it was closed—February 4, 1985; the sample contained TCE at 18,900 µg/L (Ensminger 2007; CLW 3269).

Given that the water-quality data summarized in published reports were extremely sparse (for instance, see Table 2-10), the committee expanded its evaluation to assess additional data collected in the 1980s that were summarized in CLW documents. The committee reviewed a subset of the CLW documents that contained water-quality measurement data (see Appendix C, Tables C-3 and C-4, for data abstracted from the documents) for any samples connected to the Hadnot Point water supply that were collected through February 7, 1985. The subset includes 56 samples of supply-well water collected during the period November 30, 1984-February 4, 1985, and 52 samples of mixed water collected during October 21, 1980-February 7, 1985. It also includes samples collected at locations ordinarily served by the Holcomb Boulevard water-distribution system but temporarily served by the Hadnot Point water-distribution system after a fuel spill on January 27, 1985. Appendix C contains additional information about the abstraction process.

In Table 2-11, the committee presents a summary of the analytic results for the nine contaminants of concern that it identified for the Hadnot Point water system. Summary statistics of concentrations were computed only for the samples that had specific values recorded—samples listed as "non-detect," "detect," or "—" were excluded in these computations—and percentiles were reported only if at least five samples contained a given compound. Sample concentrations that are listed as not quantified were recorded in the source documents as D (detect) or ND (non-detect) or were not reported (shown as "—" in the data listing). Samples in which concentrations could not be quantified are summarized in Table 2-12.

Of the nine analytes, the most prevalent compounds in mixed water samples collected from various locations in the Hadnot Point water-treatment plant and distribution system with measurable concentrations were TCE (31 quantified samples had a mean of 399 µg/L and a range of 1-1,400 µg/L) and *trans*-1,2-DCE (21 quantified samples had a mean of 169 µg/L and a range of 2-407 µg/L). PCE was quantified in four (8%) of the 52 samples. Benzene, 1,1,1-TCA, 1,1-DCE, and toluene were not detected or quantified; methylene chloride and vinyl chloride were each detected in one sample. As in the mixed water, the most prevalent compounds in potable well-water samples were TCE (17 quantified samples had a mean of 2,596 µg/L and range of 5-18,900 µg/L) and *trans*-1,2-DCE (14 quantified samples had a mean of 1,519 µg/L and a range of 2-8,070 µg/L). There was at least one detection of all contaminants except 1,1,1-TCA. In particular, there were a few high concentrations of PCE (maximum, 400 µg/L), benzene (maximum, 720 µg/L), methylene chloride (maximum, 270 µg/L), and vinyl chloride (maximum, 655 µg/L) in the potable well samples.

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TABLE 2-10 Contaminant Concentrations in Supply Wells of Hadnot Point Water System

Well	Date Removed from Service	Concentration, µg/L[a]							
		TCE	PCE	Benzene	*Trans*-1,2-DCE	1,1-DCE	Methylene Chloride	Toluene	Vinyl Chloride
602	Nov. 30, 1984	1,600	24	120	630	2.4	—	5.4	18
601	Dec. 6, 1984	210	5	ND	88	ND	ND	ND	ND
608	Dec. 6, 1984	110	ND	3.7	5.4	ND	ND	ND	ND
634	Dec. 14, 1984	ND	ND	ND	2.3	—	130	—	ND
637	Dec. 14, 1984	ND	ND	ND	ND	—	270	—	—
651	Feb. 4, 1985	3,200	386	—	3,400	187	—	—	655
652	Feb. 8, 1985	9	ND	—	ND	ND	—	—	ND
653	Feb. 8, 1985	5.5	ND	—	ND	ND	—	—	ND

[a]Detection limit for each contaminants was 10 µg/L.
Abbreviation: ND = not detected.
Source: GAO 2007.

In Table 2-13, the committee provides a detailed summary of Hadnot Point area supply wells that had at least one nonzero value for at least one of the nine analytes. It shows the well number, IR sites near the well, well depth, screen interval, a summary of measured VOC concentrations, and dates of operation. Some of the water-supply samples were collected after individual wells were closed, and it is important to note that pumping can affect the degree of contamination in wells. Of the 10 wells summarized in Table 2-13, eight were closed from late 1984 through early 1985 (GAO 2007). Well 651 had the highest contamination, with detectable concentrations of TCE in all the reported samples. Well 651 also had relatively high readings of *trans*-1,2-DCE, PCE, and vinyl chloride. Wells 602 and 634 each had one sample with a TCE concentration above 1,000 µg/L (1,600 and 1,300 µg/L, respectively).

Hadnot Point Supply-Well Operation and Implications

The supply wells for the Camp Lejeune water system were on a cycled pumping schedule; that is, generally only some of the wells were pumping raw water to the water-treatment plant at any given time (GAO 2007). Typically, pumps at various wells are scheduled to cycle on or off at different times during the day, so a dynamic mixture of water from different wells flows into the water-treatment plant and into the distribution system serving residences and other facilities. Well cycling is important to consider if one wants to understand the presence of contaminants in the distribution system inasmuch as concentrations of contaminants might vary greatly from day to day or even over the course of a single day, depending on whether contaminated wells were pumping.

The committee is aware of one document (CLW 6950) that summarizes well-cycling information during a period assumed to be November 28, 1984-February 4, 1985 (Marine Corps, personal commun., February 26, 2008). The document lists Hadnot Point well numbers and some date information (calendar days without accompanying months or years) with an "X" whenever a well pumped on a given date. If the inferred dates are correct, the document shows that individual wells operated on the average for 38% of the days over the 69-day period, with a large range of operation frequency (individual wells pumped on 0-96% of the days). On the average, 16 wells pumped each day; the range was 9-27. In Table 2-14, the committee presents the well-cycling information in combination with water-sampling data from the same

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TABLE 2-11 Hadnot Point Water-Supply Quality Measurements (October 1980-February 1985)

Water Source	Contaminant	No. Samples[a]		% Samples Quantified	Individual Samples, µg/L	Summarized Data on Samples with Quantified Values, µg/L[b]					
		ND/NQ[c]	Quantified			Mean	Min	25th Percentile	Median	75th Percentile	Max
Supply wells	TCE	39	17	30		2,596	5	13	210	1,300	18,900
	PCE	48	8	14		153	2	5	17	392	400
	Benzene	50	6	11		180	2	4	62	230	720
	1,1,1-TCA	56	0	0							
	1,1-DCE	54	2	4	2; 187	95					
	trans-1,2-DCE	42	14	25		1,519	2	9	165	700	8,070
	MC	50	6	11		78	7	10	26	130	270
	Toluene	54	2	4	5; 12	9					
	VC	51	5	9		205	7	18	168	179	655
Mixed water	TCE	21[d]	31	60		399	1	19	200	849	1,400
	PCE	48[d]	4	8	1; 4; 8; 15	7					
	Benzene	52	0	0							
	1,1,1-TCA	52	0	0							
	1,1-DCE	52	0	0							
	trans-1,2-DCE	31	21	40		169	2	9	150	321	407
	MC	51	1	2	54	54					
	Toluene	52	0	0							
	VC	51	1	2	3	3					

[a]Samples in this table listed separately in Appendix C, Tables C-3 and C-4. Samples treated as distinct if reported on separate laboratory reports; in some cases, multiple samples reported from same location on same date, but it is not known whether these were duplicate samples.
[b]Sample concentrations presented as summary statistics if more than four samples were quantified. Quantified samples listed individually if four or fewer samples quantified.
[c]ND/NQ samples do not have reported concentrations for various possible reasons, including that they were not measured, were not detected, or were recorded merely as detected. See Table 2-12 for additional information about these samples.
[d] Concentrations measured in seven of 11 samples collected before 1984 were assumed to be detected on basis of notes on laboratory reports and inferences from later laboratory reports.
Abbreviations: DCE = dichloroethylene; MC = methylene chloride; ND = not detected; NQ = not quantified; TCA = trichloroethane; VC = vinyl chloride.

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TABLE 2-12 Summary of Data on Water Samples[a] from Hadnot Point Water System Recorded As Not Detected or Not Quantified in Table 2-11

Water Source	Contaminant	ND/NQ	ND/NQ Category			
			Reported as Detected	<2.0 or <1 µg/L	ND	No data
Supply wells	TCE	39			39	
	PCE	48			48	
	Benzene	50			50	
	1,1,1-TCA	56			56	
	1,1-DCE	54			54	
	*trans*1-2,DCE	42			42	
	MC	50			50	
	Toluene	54			54	
	VC	51			51	
Mixed water	TCE	21[b]	7	6	7	1
	PCE	48[b]	7	2	12	27
	Benzene	52			14	38
	1,1,1-TCA	52			14	38
	1,1-DCE	52			14	38
	*trans*1-2,DCE	31		7	10	14
	MC	51			13	38
	Toluene	52			14	38
	VC	51			13	38

[a]Data listed separately in Appendix C (Tables C-3 and C-4). Samples treated as distinct if reported on separate laboratory reports; in some cases, multiple samples reported from same location on same date, but it is not known whether these were duplicate samples.
[b]Concentrations measured in seven of 11 samples taken before 1984 assumed to be detected on basis of notes on laboratory reports and inferences from later laboratory reports.
Abbreviations: DCE = dichloroethylene; MC = methylene chloride; ND = not detected; NQ = not quantified; TCA = trichloroethane; VC = vinyl chloride.

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TABLE 2-13 Characteristics of the Hadnot Point Supply Wells With At Least One Contaminated Sample Taken Between October 1980 and February 1985

Well[a]	IR Site[b]	Well Depth, ft[c]	Screened Intervals, Number (Range, ft)[c]	No. Water Samples[d]	Contaminants, µg/L[d]								Year Well Started	Date Well Shut Down[e]
					TCE	PCE	*Trans*-1,2-DCE	1,1-DCE	MC	VC	Benzene	Toluene		
601	9, 78	195	4 (45-195)	3	26 210 230	ND 4 5	9 88 99		ND ND 10				1941	Dec. 6, 1984
602	9, 78	160	5 (70-160)	4	38 340 540 1,600	ND ND 2 24	74 230 380 630	ND ND ND 2		ND ND ND 18	ND 120 230 720	ND ND 5 12	1941	Nov. 30, 1984
603	78	195	5 (70-195)	3	ND ND 5				ND ND 7				1941	
608	78	161.5	4 (61.5-161.5)	3	9 13 110		ND 2 5		ND ND 14		2 4 4		1942	Dec. 6, 1984
634	9, 78	225	10 (63-225)	3	ND ND 1,300	ND ND 10	ND 2 700		ND ND 130	ND ND 7			1959	Dec. 14, 1984
637	6, 9, 78, 82	172	5 (90-172)	3					ND ND 270				1969	Dec. 14, 1984
642	9, 78	210	5 (112-196)	3					ND ND 38				1971	
651	9, 82	199	3 (125-194)	3[f]	3,200 17,600 18,900	386 397 400	3,400 7,580 8,070	ND ND 187		168 179 655			1971	Feb. 4, 1985
652				1	9								1972	Feb. 8, 1985
653	6, 82	270		1	6								1978	Feb. 8, 1985

[a]Wells installed before March 1, 1985. Many other wells were operating before March 1, 1985, but are not included in list because contaminants not detected.
[b]See Figure 2-6.
[c]Data abstracted from Baker Environmental, Inc (1993a,b).
[d]Samples listed in Appendix C, Table C-4. All readings are shown for individual compounds with at least one detection.
[e]Well-closing dates reported in GAO (2007).
[f]Includes two samples collected on same date and listed as "duplicates" on secondary source document.
Abbreviations: DCE = dichloroethylene; IR = installation restoration; MC, methylene chloride; ND = not detected; PCE = perchloroethylene; TCE = trichloroethylene; VC = vinyl chloride.

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TABLE 2-14 Concentrations of Contaminants in Mixed Water Samples Collected from Hadnot Point Water-Distribution System During Period of Documented Well Cycling[a]

Date	No. Water Samples[c]	Average Concentration, µg/L[b]				No. Wells Pumping	Wells[d]
		TCE	PCE	*trans*-1,2-DCE	MC		
Dec. 4, 1984	2	123	2	49	0	21	603, 608, 634, 637, 642, 652[e]
Dec. 10, 1984	1	2	0	2	0	10	637, 652
Dec. 13, 1984	1	0	0	0	54	18	652, 653
Dec. 14, 1984	1	0	0	0	0	18	652
Dec. 15, 1984	1	0	0	0	0	15	642, 652
Dec. 16, 1984	1	0	0	0	0	13	642, 652
Dec. 17, 1984	1	0	0	0	0	13	603, 642, 652
Dec. 18, 1984	1	0	0	0	0	13	603
Dec. 19, 1984	2	1	0	0	0	13	603
Jan. 29, 1985	3	463	[f]	[f]	[f]	18	603, 642, 651, 653
Jan. 31, 1985	14	618	[f]	225	[f]	19	603, 642, 651, 652, 653

[a]Dates estimated to be November 28, 1984, through February 4, 1985.
[b]All nondetected values treated as having concentrations of 0.
[c]The location from which the samples were taken are provided in Appendix C, Table C-3.
[d]Wells with at least one detected analyte that were pumping on same day or up to 2 days before date specified.
[e]Well 651 pumped 3 days before these samples were taken.
[f]Contaminant not measured or reported for mixed water samples collected on this date.
Abbreviations: DCE = dichloroethylene; MC = methylene chloride; PCE = perchloroethylene; TCE = trichloroethylene.

period to ascertain the potential effect of well cycling on measured contaminant concentrations. To illustrate the effect of well cycling on mixed-water contamination, the committee made the highly conservative assumption that all "non-detect" samples had zero concentrations of the listed contaminants. The table indicates that 10-21 wells delivered raw water to the water-treatment plant on days when at least one mixed-water sample was analyzed. At least one well with demonstrated contamination pumped on the same day or previous 2 days from the dates when water samples were collected, but contamination in the mixed water was not detected on all dates on which a sample was collected.

TCE, PCE, *trans*-1,2-DCE, and methylene chloride were detected in mixed-water samples taken during November 28, 1984-February 4, 1985. Benzene, 1,1-DCE, toluene, and vinyl chloride—all of which were reportedly detected in the Hadnot Point supply-well samples—either were not included in the laboratory analysis or were not detected in measurable concentrations in mixed-water samples during that period. The two dates with the highest average TCE concentrations (463 and 618 µg/L) were the dates when well 651 was supplying water to the system on the current and/or previous 2 days; this suggests that well 651 was an important source of contamination of the Hadnot Point water-supply system. In addition, the 14 mixed-water TCE measurements in samples from one of those days (January 31, 1985) had a range of 24-1,148 µg/L.

Hadnot Point Area Monitoring Wells

The committee focused its review on some of the earliest deep-groundwater monitoring data available from the remedial-investigation reports for waste sites 6, 9, 78, and 82 in the Hadnot Point area (Baker Environmental, Inc 1994). Monitoring wells were used to collect water samples from depths of about 148-153 ft below ground surface. Screens (elevations of water-intake portals in the well pipe) in

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most of the wells that supplied water to the Hadnot Point water system were installed at depths of 60-190 ft below ground surface. Each supply well had three to five screens. Thus, the analytic results on water samples taken from deep monitoring wells should be representative of contamination of the Castle Hayne aquifer at a depth consistent with water withdrawal from the water supply, albeit at least 7 years after the discovery of contaminants in the Hadnot Point supply wells.

The remedial investigation of site 78 was preceded by several investigations, including an initial assessment study (1983) that identified the groundwater contamination and a confirmation study (1984-1988) that documented the presence of VOCs related to fuels and solvents in the groundwater. A later supplemental characterization step study (1990-1991) and pre-investigation study (1992) set the stage for the systematic sampling effort for the remedial investigation in 1992 (Baker Environmental, Inc 1994).

Groundwater in the vicinity of sites 6 and 82 was also sampled as part of the confirmation study (1984-1988). The remedial investigation of sites 6 and 82 included three rounds of groundwater sampling, conducted in two phases: phase 1 in 1992 and phase 2 in 1993 (Baker Environmental, Inc 1993). The investigation at each site, including groundwater sampling and analyses, continued after the publication of the remedial-investigation reports. The committee judged that the focus on the remedial-investigation reports for Hadnot Point sites was justified because they provided a reasonable snapshot of contamination closest to the period of interest.

For the remedial investigation, groundwater samples were generally analyzed for two suites of common chemical contaminants known as the "target compound list" (TCL) and the "target analyte list" (TAL). The results of the detections are summarized below; a more complete discussion is presented in Appendix C (Table C-5).

The monitoring-well data identify TCE, phenol, benzene, *cis*- and *trans*-1,2-DCE, and 1,1-DCE as the most prevalent contaminants in groundwater at the locations and screened depths of the wells. Other contaminants with multiple detections were arsenic, cadmium, 1,2-dichloroethane, and PCE. TCE, phenol, and *cis*- and *trans*-1,2-DCE had the highest prevalence of concentrations measured above their limits of detection.

Concentrations reported in the remedial-investigation reports varied widely among the well sites. For example, the concentrations of TCE in 11 samples ranged from 1.3 to 58,000 µg/L. Similarly, detections of *trans*-1,2-DCE ranged from 1 to 26,000 µg/L, of phenol from 2 to 22,000 µg/L, and of benzene from 6.7 to 35 µg/L. The most contaminated locations were near supply well 651, next to sites 6 and 82.

At most locations, shallow groundwater (sampled at a depth of less than 25 ft) had the greatest number of contaminant detections, including such TCL chemicals as TCE (0.5-2,100 µg/L) and fuel constituents benzene (not detected to 9,200 µg/L), toluene (not detected to 18,000 µg/L), ethylbenzene (not detected to 3,000 µg/L), xylenes (not detected to 16,000 µg/L), and naphthalene (not detected to 260 µg/L) (Baker Environmental, Inc 1993, 1994). TAL metals that were commonly detected in shallow water, with some samples at exceedingly high concentrations relative to EPA's current MCLs, were arsenic (405 µg/L), barium (1,200 µg/L), chromium (858 µg/L), lead (126 µg/L), and manganese (714 µg/L) (Baker Environmental, Inc 1993, 1994). Only five wells of intermediate depth (about 50-75 ft) were sampled as part of the remedial investigation, and detected chemicals were generally measured at concentrations below risk-based criteria.

The results of groundwater sampling and analysis with monitoring wells provide additional information regarding the presence of contaminants in the aquifer. In many ways, the data are secondary to the analytic results on samples taken from the supply wells or the tap, at least for the purposes of understanding historical exposures. However, because the available information on such samples is sparse, it is important to consider all available data, including those from monitoring wells.

Contaminants of Concern in the Hadnot Point Water Supply

The paucity of water-quality measurements of the Hadnot Point water supply, both temporally and spatially, makes it difficult to characterize the contaminants of concern accurately. Multiple waste

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and operational sites have contributed to the groundwater contamination since the 1940s, so the nature of the contamination has probably varied. The few available measurements were taken during the 1980s and 1990s, decades after the contamination could have begun. The principal contaminants discovered in the wells that supplied Hadnot Point in the early 1980s were TCE and PCE. TCE, phenol, benzene, *cis*- and *trans*-1,2-DCE, and 1,1-DCE were the most prevalent contaminants in samples collected in 1992 and 1993 from deep monitoring wells. Other contaminants with multiple detections in monitoring wells were arsenic, cadmium, 1,2-dichloroethane, and PCE . The chemical 1,1,1-TCA, which was on the preliminary list of contaminants of concern compiled by the committee, is given only cursory attention in this report because it was not observed in any Hadnot Point water-quality samples collected before February 8, 1985. However, 1,1,2-trichloroethane was detected in one sample from a monitoring near well 651 at 5.8 µg/L (see Appendix C, Table C-5).

Groundwater Fate and Transport Model for Hadnot Point

ATSDR has proposed that the methods that were used for Tarawa Terrace be applied to reconstruct the historical contamination of water supplied by the Hadnot Point water-treatment plant (Maslia 2008). The proposed reconstruction will simulate the groundwater concentrations of TCE, PCE, and BTEX (benzene, toluene, ethylbenzene, and xylene). The preliminary data-screening efforts started in January 2008, and work is expected to be completed on October 2009. The study includes 10 technical tasks: analysis of data from16 sites; computation of mass of PCE, TCE, and BTEX at about six major sites; review of capacity histories of about 100 wells; statistical analysis of existing data; fate analysis; fate and transport model selection; grid design and data input; fate and transport analysis; water-distribution system analysis; and uncertainty analysis. ATSDR is also committed to providing updates on its progress by participating in external progress meetings and Community Assistance Panel meetings and by preparing and disseminating data analyses and model simulations. On the basis of work already carried out, ATSDR also indicated the following (Maslia 2008):

- Discovery of new or updated site information after the second quarter of FY 2008 that substantially alters baseline information may add time to the current timeline estimate.
- Because of the expanse of the area being modeled, computational time for fate and transport analyses may be longer than previously estimated. When model selection and grid design have been completed, a more refined estimate of required computational time will be made.

Earlier in this chapter, the committee identified several limitations in the Tarawa Terrace historical reconstruction and groundwater modeling. Because the contamination at Hadnot Point is more complex, the limitations and difficulties related to such modeling will be greater.

WATER USE PATTERNS AND BEHAVIORS

Place of residence is a key determinant of exposure to contaminants in water at Camp Lejeune, but individual behavior—including water consumption, showering or bathing patterns, and other water-related behaviors (such as dishwashing)—also would influence the degree of exposure. The committee is not aware of any historical information that documents individual water-use patterns and behaviors of residents of base housing. Some information on typical water use and other factors that affect individual exposure is available (EPA 1997, 2008). Some specific information on the Camp Lejeune population is being sought as part of ATSDR's case-control study focused on birth defects and childhood cancer outcomes (see Chapter 8). However, as in all retrospective epidemiologic studies of water-supply contamination, the validity of such information is open to question given that it requires retrospective recall of water-consumption habits and water-related behaviors that occurred decades earlier, increasing the like-

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lihood that error due to recall bias could be substantial. The contaminated water systems also supplied nonresidential areas of the base, including schools, workplaces, recreational areas, and a hospital. Water-use patterns and behaviors in those setting are expected to differ substantially from practices in residences. In addition, people could have been exposed to contaminated water at multiple locations, for instance, in both residential and nonresidential settings.

EXPOSURE PATHWAYS

Although most attention has focused on the ingestion of contaminated water, additional exposure pathways were possible, including the inhalation of chemicals that have volatilized from standing water in toilets or from faucet or shower water and dermal exposure from showering and washing. Although there are no contemporaneous data on the Camp Lejeune population, exposure via inhalation and dermal absorption of VOCs from water used for household purposes has been shown experimentally to account for as much exposure as that from drinking the water (see Chapter 3). The intrusion of vapor from shallow contaminated groundwater into homes and offices is yet another possible inhalation-exposure pathway. ATSDR's simulation efforts indicate a potential for vapors from plumes at Tarawa Terrace to have entered buildings, including an elementary school and family housing (Maslia et al. 2007). EPA recently examined the possibility of vapor intrusion at the Tarawa Terrace Elementary School and several housing units and did not find any current problems (EPA 2007a,b). Any estimates of past exposure to contaminated groundwater should consider all exposure pathways.

AFFECTED STUDY POPULATION

Residential history in housing areas served by the contaminated water supplies during the period of contamination is an important determinant of exposure. There are two major categories of housing at Camp Lejeune: family housing for personnel on assignment to Camp Lejeune and barracks for enlisted personnel rotating through the base for training. The committee was provided with an estimated number of residential houses on Camp Lejeune by water-supply system in any given year from 1941 to 2000 by the Marine Corps (Appendix C, Table C-6). The first year with substantial residential water service was 1943, in which an estimated 919 units were served by the Hadnot Point water system, the first to serve a residential development on the base other than a barracks. Large increases in the total number of family-housing units on the base occurred in 1952, with the construction of Tarawa Terrace housing (3,065 units); in 1958, with the construction of Marine Corp Air Station housing (3,500); in 1961, with the construction of Berkeley Manor and Paradise Point Capehart housing (4,177); and in 1978, with the construction of Watkins Village housing (4,550). Substantial shifts in the water-supply source for residential housing occurred in 1972 when about 1,886 housing units were transferred from the Hadnot Point water system to the Holcomb Boulevard system and in 1987 when about 1,955 housing units were transferred from the Tarawa Terrace system to the Holcomb Boulevard system. Translating the number of housing units into the size of the population that may have been exposed would require knowledge of the number of residents per household or at least the number of residents by housing area in each year. To translate that into potential years of residential exposure for a given person or household, the duration of residence on the base would need to be ascertained. To assess potential exposure of that person or household to specific contaminants in the water supply, more accurate information on the location and period of residence would need to be ascertained. Information on the population size or typical duration of residence of personnel assigned to barracks was not available.

Potential exposures in nonresidential settings should also be considered. Such exposures may occur in schools and job locations on the base. Table 2-15 presents potential sites of nonresidential exposure to contaminants from the Tarawa Terrace and Hadnot Point water systems in 1943-1985. No information was available on the number of persons in occupational, school, or day-care settings with potential exposure to contaminated water.

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EXPOSURE ASSESSMENT IN STUDIES OF HEALTH EFFECTS OF WATER-SUPPLY CONTAMINATION AT CAMP LEJEUNE

ATSDR has completed two epidemiologic studies of water-supply contamination at Camp Lejeune (ATSDR 1998; Sonnenfeld et al. 2001). They focused on prenatal outcomes, including mean birth weight, small for gestational age, and preterm birth. The studies were limited to singleton live-born infants (with estimated gestational ages of 20 weeks or more) whose mothers resided in base housing for at least 1 week before giving birth in January 1, 1968-December 31, 1985. The earlier study (ATSDR 1998) also included stillborn infants. The results of those studies are presented in Chapter 8, and this section briefly summarizes the exposure assessments that were used in each.

The 1998 ATSDR study evaluated residents of Tarawa Terrace and Hadnot Point, whereas the 2001 Sonnenfeld et al. study evaluated only residents of Tarawa Terrace. In both studies, exposure was defined by place of residence at delivery and ascertained by linking birth records to the base's family-housing records.

In the ATSDR study, residents of trailer parks were excluded because of the incompleteness of housing information and the inability to identify their water source. Infants whose mothers resided at Tarawa Terrace for at least 1 week before giving birth were classified as exposed. Also included in the exposed group were infants whose mothers received water from the Hadnot Point water system in the Hospital Point housing areas or resided in the service area of the Holcomb Boulevard water system and were pregnant for at least 1 week in a 12-day period in January 27-February 7, 1985. During that period, Hadnot Point water served or was present in the Holcomb Boulevard system for operational reasons. Infants whose mothers were residents in other base family housing (the Marine Corps Air Station, Rifle Range, and Courthouse Bay housing areas) were classified as unexposed, as were infants whose mothers lived in areas served by the Holcomb Boulevard water system (defined as Berkeley Manor, Midway Park, Paradise Point, and Watkins Village housing areas) during the study period other than the 2-week period in winter 1985 when the Holcomb Boulevard system received contaminated water from the Hadnot Point

TABLE 2-15 Potential Sites of Nonresidential Exposure to Contaminants in the Tarawa Terrace and Hadnot Point Water Systems, 1943-1985

Exposure Scenario	Years Contaminated
Employment at Hadnot industrial area or other workplace	Unknown-1985
Employment location served by Tarawa Terrace water system	1957-1985
Tarawa Terrace Elementary School	1957-1985
Tarawa Terrace day care	1957-1985
Hadnot Point-Holcomb Boulevard area schools • Russell School, 1943-1987 • Old high school/middle school, 1963-1987 • Berkeley Manor Elementary School, 1963-present • Stone Street Elementary School, 1959-present • Midway Park Elementary School, 1952-present	Until 1972; intermittent linkages with the Hadnot Point system; and during a 2-week period in 1985
Hadnot Point-Holcomb Boulevard area day-care services • New hospital, 1983-1987 • Building 712, 1966-1982 • Building LCH4025, 1960-1987 • Building 799, 1953-1987 • Building 2600, unknown-1987 • Building 899, 1985-1987 • Building 1200, 1942-1987	Until 1972; intermittent linkages with the Hadnot Point system after 1972; and during a 2-week period in 1985

Source: Marine Corps, personal commun., December 4, 2007.

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system. ATSDR also computed the number of weeks that a mother lived in the residence specified on the birth certificate on the basis of information about occupancy dates from the housing records, which were then categorized and used in analyses to explore the effects of duration of exposure on the adverse pregnancy outcomes that were under investigation. However, ATSDR discovered after the study was completed that the Holcomb Boulevard water-treatment plant had been in operation since 1968 (rather than 1972), so pregnant mothers receiving water from that system in 1968-1972 were incorrectly classified as "unexposed." A reanalysis to correct that error is planned; exposure estimates from the water-modeling study (http://www.atsdr.cdc.gov/HS/lejeune/erratum.htm) will be used.

In the Sonnenfeld et al. study, infants born to mothers living at Tarawa Terrace for at least 1 week before delivery were classified as exposed. With the exception of people who were excluded because they lived in base trailer parks or in areas served by distribution systems outside Tarawa Terrace that were also contaminated with TCE, all other infants whose mothers resided in base family housing were classified as unexposed. Misclassification of women as unexposed if they resided in areas served by the Holcomb Boulevard water system and were pregnant in 1968-1972 also affected this study. For each birth, length of maternal residence at Tarawa Terrace before delivery was computed by using dates of occupancy from the housing records and then categorized and used as another surrogate of exposure to explore effects on prenatal outcomes.

Given the nature of the contamination at Camp Lejeune, the committee found the application of broad classifications of exposure based on place and duration of residence to be an appropriate approach for assessing exposure in the studies described above. Historical reconstruction and groundwater modeling at Tarawa Terrace have provided additional characterization of potential exposure to PCE and an estimated timeframe for the contamination, but it is questionable whether the additional information improves the exposure assessment for epidemiologic studies. Retrospective data on time-activity patterns of water use and water-related behaviors could improve exposure assessment but will be of questionable accuracy because the assessment is for periods that extend 20 years or more into the past.

CONCLUSIONS

The Tarawa Terrace and Hadnot Point water supply systems were contaminated with VOCs—particularly TCE, PCE, and DCE—for decades ending in the middle 1980s. Most of the organic contaminants originated from DNAPLs, which have the potential to contaminate large volumes of groundwater over long periods. The hydrogeologic data indicate a high potential for contaminants from surface sources to migrate to water-supply wells in some areas of the base. The absence of a continuous impermeable barrier between the surface (source area) and the Castle Hayne aquifer (primary aquifer) supports the field observations that show contaminants in deep monitoring wells at the same depth as the water-supply wells.

The exact extent of the contamination at Camp Lejeune cannot be documented with certainty, but it is known that a few highly contaminated wells supplied water to the Tarawa Terrace and Hadnot Point systems and that the contaminated wells were in operation for multiple years. The contaminant concentrations in the water-supply system varied because well pumping was cycled (the contaminated wells were not operated continuously, so there were fluctuations in contaminant concentrations). The qualitative evidence suggests that the magnitude of groundwater contamination was much higher in the Hadnot Point system than in the Tarawa Terrace system. It is also known that the Hadnot Point system supplied water to the Holcomb Boulevard water-supply area before 1972 and periodically after 1972. Widespread water-supply contamination in other water systems on the base was not evident from available documentation, but the committee's review was too limited to be conclusive in this regard.

The fundamental problem in estimating exposure to contaminants in the water-supply systems of Tarawa Terrace and Hadnot Point quantitatively is the lack of information on water quality and treatment-system operation during the period of contamination. There are no water-quality data for the period before the 1980s, and this leaves a 40-year period for which the extent of water-supply contamination is un-

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documented. In addition, little documentation is available on water-treatment techniques, which would shed light on the efficiency of contaminant removal during treatment. Also lacking is information on well cycling, which is important for documenting when contaminated wells were pumping raw water into the system. For those reasons, any estimates of water-supply contamination must rely on unverifiable assumptions.

ATSDR applied best practices and cutting-edge modeling approaches to predict the complex groundwater-contamination scenario at Tarawa Terrace. The ultimate outcome of the modeling was averaged monthly predictions of the concentrations of contaminants in the water supply to which people could have been exposed. Although ATSDR recognized and tried to account for the limitations and uncertainties associated with developing its models, it is extremely difficult to obtain quantitative estimates of historical levels of exposure to PCE and its degradation products reliably on a monthly basis. Reporting such model predictions without clear error bounds gives the impression that the exposure of former residents and workers at Tarawa Terrace during specific periods within a given year can be accurately defined. It is the committee's judgment that ATSDR's model is suitable only for estimating long-term exposure qualitatively. From that perspective, a single exposure category of "exposed" appears to be applicable for persons residing or working at Tarawa Terrace at any time during 1957-1985.

Efforts at historical reconstruction of exposures at Hadnot Point will be even more problematic. The contamination scenario at Hadnot Point is so complex that the committee judges that only crude estimates of contaminant concentrations in the water supply can be obtained.

RECOMMENDATIONS

The history of water-supply contamination at Hadnot Point is much more complex than the history of that at Tarawa Terrace because of the multiplicity of sources and contaminants and the ill-defined period of contamination. Therefore, the committee recommends the use of simpler approaches (such as analytic models, average estimates based on monitoring data, mass-balance calculations, and conceptually simpler MODFLOW/MT3DMS models) that use available data to rapidly reconstruct and characterize the historical contamination of the Hadnot Point water-supply system. Simpler approaches may yield the same kind of uncertain results as complex models but are a better alternative because they can be performed more quickly and with relatively less resources, which would help to speed-up the decision-making process.

As needed, and if available, better field characterization and details (such as active supply wells and cycling schedules, geologic data, and source characteristics) may be added to the conceptual models to improve understanding of transport at selected locations where potential exposure was high. Detailed MT3DMS modeling studies should be performed only for selected sites (using locally-refined grids) and only after establishing a priori the clear need, objectives, and expected outcomes for such studies. On the basis of the results of the Tarawa Terrace models, application of cutting-edge research codes for groundwater modeling (such as PSOpS and TechFlow) is unlikely to reduce uncertainty in the Hadnot Point exposure scenarios, which are expected to be much more complex than at Tarawa Terrace.

Future modeling efforts should also be aided by additional field information about the physical and chemical characteristics of the sources and receptors (aquifers). Specifically, the hydrogeologic characterization of the recharge zones of the primary aquifer that was and is the source of water for the water-supply systems at Camp Lejeune should be determined. For example, the extent and characterization of the Castle Hayne confining unit are critical for understanding the potential for hydraulic connectivity between the waste sites identified and the source aquifer for the water-supply wells over the period of potential exposure (1943-present). It is well documented that the confining layer is neither continuous nor confining in all areas beneath the Camp Lejeune geographic boundary.

The committee's effort to evaluate potential exposures to contaminants in the Tarawa Terrace and Hadnot Point water systems was hampered by the fact that the available data on water quality of those systems was found in hundreds of documents. Most of the documents are publicly available on line, but

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they were not readily searchable or cataloged in an organized fashion for research. To facilitate future exposure-assessment efforts, the committee strongly recommends that a comprehensive, accessible database of water-quality measurements (including data from remedial investigations) be created and maintained. Such a database should include information on sample location, date, analytes measured, laboratory quality-control information (including limits of detection), and other information relevant to exposure assessment that relies on environmental samples collected in the course of investigating water, soil, and air quality at Camp Lejeune.

Because of the sparseness of water-quality data and the insufficient ability of water-quality modeling to make up for the absence of information, most exposure estimates in epidemiologic studies at Camp Lejeune will rely heavily on unverifiable assumptions and projections. Therefore, the most useful exposure assessment will likely be relatively crude and based for the most part on ascertaining the most likely time period and location (water supply system) of contamination, typical locations the study participant spent time on the base (for example, residence, school, daycare, workplace), and crude categorization of personal water-use activities during the exposure period.

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3

Systemic Exposures to Volatile Organic Compounds and Factors Influencing Susceptibility to Their Effects

When evaluating health effects of chemicals, it is important to understand how they enter and are distributed in the body (systemic exposure) and how the body handles them and their metabolites. This chapter reviews general issues related to evaluation of exposure to volatile organic compounds (VOCs) in that context. It considers characterization of differences between laboratory animals and humans and implications for the interpretation of the animal-toxicology literature that is presented in Chapter 4, identification of human populations that might be more susceptible than others to the effects of the primary contaminants of concern, and interactions that might result from exposure to mixtures of chemicals.

VOCs are the focus of this chapter because the primary water contaminants at Camp Lejeune and specified in the study charge are in this class of compounds. As noted in Chapter 2, other contaminants have been detected in the water supplies, so exposures were more complex than just VOC mixtures. However, for the purposes of this report, the review has been restricted to the primary VOC contaminants of concern.

ENVIRONMENTAL CONTAMINATION

The major drinking-water contaminants of interest at Camp Lejeune are volatile organic chemicals (VOCs), mainly trichloroethylene (TCE) and tetrachloroethylene (perchloroethylene, PCE) but also vinyl chloride, methylene chloride, benzene, toluene, *cis*- and *trans*-1,2-dichloroethylene (DCE), and 1,1-DCE (see Chapter 2). All those except benzene are halogenated, short-chain aliphatic hydrocarbons (halocarbons); benzene is an aromatic hydrocarbon. The water solubility of these compounds increases with decreasing numbers of carbon or halogen atoms. The maximum water solubilities of PCE and TCE at 25°C, for example, are 150 and 1,366 mg/L, respectively. Volatility increases with decreasing molecular weight, varying from 18.5 mm Hg for PCE to 74 mm Hg for TCE at 25°C (ATSDR 1997b,c).

Widespread use of TCE and other VOCs has resulted in their frequent escape into the environment (Wu and Schaum 2000). Figure 3-1 illustrates the pathways by which environmental media are contaminated and how people may be exposed. Most VOCs that enter the environment do so by evaporation during their use or discharge. Concentrations in air in the immediate vicinity of point sources may be high, but winds rapidly dilute and disperse the vapors (from nondetectable to nanograms per cubic meter of air). Migration of VOCs from subsurface soil or groundwater into the air in basements (vapor intrusion) also occurs. There does not appear to be a wide-scale assessment of the importance of the soil vapor intrusion pathway for human exposure to VOCs. The contribution of different variables to TCE permeation is described in a laboratory simulation by Fischer and Uchrin (1996), and another tracer gas was used to develop a mathematical model for the phenomenon (Olson and Corsi 2001).

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Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects

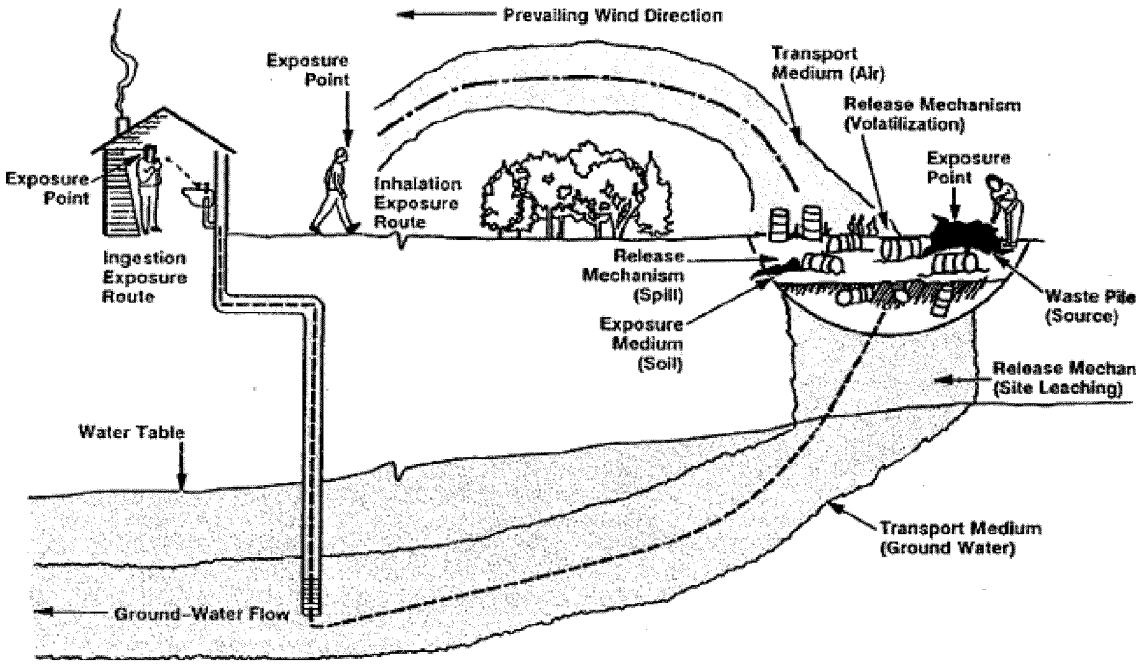


FIGURE 3-1 Environmental contamination from solvents and exposure pathways. Source: EPA 1989.

Contamination of drinking-water supplies is of greater health concern. In past years, halocarbons were generally regarded as water-insoluble. It is now recognized that they are soluble in water to a small extent. Maximum solubilities, for example, range from 150 mg/L (or parts per million) for PCE to 4,800 mg/L for methylene chloride. Concentrations typically found in finished drinking water in the United States range from parts per trillion to parts per billion (Moran et al. 2007).

VOCs are found as contaminants of surface water and groundwater. Concentrations diminish rapidly after VOCs enter bodies of water, primarily because of dilution and evaporation. Halocarbons rise to the surface or sink to the bottom, depending on their density. Halocarbons on the surface largely evaporate. The movement of halocarbons on the bottom depends on their solubilization in water and their mixing by currents or wave action; mixing causes them to reach the surface. Hydrocarbon solvents spilled onto the ground largely evaporate, although some can permeate soil and migrate through it until reaching groundwater or an impermeable layer. Migration of solvents through sandy soil of low organic content is most rapid and extensive (Munnecke and Van Gundy 1979). Solvents in groundwater tend to remain trapped until the water reaches the surface, although some are subject to microbial modification. PCE and TCE, for example, undergo reductive dehalogenation by microorganisms to a small extent to *cis*- and *trans*-1,2-DCE, vinyl chloride, and other products (Smith and Dragun 1984; McCarty 1993). Thus, halocarbon-contaminated groundwater usually contains a relatively high proportion of parent compounds and small amounts of microbial degradation products.

EXTERNAL EXPOSURE

People are exposed to halocarbons and other VOCs in water by three major routes: inhalation, skin contact, and ingestion. A number of studies have looked at the relative importance of those routes. Weisel and Jo (1996) based estimates of internal doses of TCE and chloroform received from showering on results of experiments with human subjects. They concluded that inhalation and dermal exposure resulted in an internal dose of each chemical comparable with the dose ingested in 2 L of water. Gordon et

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al. (2006) conducted a detailed investigation of the contribution of household water use to internal doses of chloroform and other trihalomethanes. Showering and bathing resulted in the highest blood and exhaled-breath concentrations of chloroform in human subjects in household settings; inhalation and percutaneous absorption were also found to be important routes of exposure. Giardino and Andelman (1996) reported that the temperature of water had a dominant effect on volatilization of TCE and chloroform during showering. Some 80% of TCE and 60% of chloroform were released from hot shower water. Haddad et al. (2006) used a physiologic model to assess different home exposure scenarios and concluded that ingestion contributed less than 50% of the total absorbed dose of TCE. Thus, systemic absorption from the lungs, skin, and gastrointestinal tract should all be taken into account in estimating internal doses that result from use of water supplies contaminated with VOCs.

INTERNAL EXPOSURE

The concept of dose has been refined during the last 15-20 years. The amount of a chemical to which a person is exposed is now termed the external exposure or administered dose. Absorption into the blood may be partial or complete, depending on the chemical and route of exposure. The amount of a chemical absorbed systemically from the lungs, gastrointestinal tract, and skin is termed the absorbed dose or internal dose. The amount of a chemical that reaches an organ or tissue where a toxic effect occurs is termed the target-organ dose. It is necessary here to specify the amount of the toxicologically active forms of the chemical. In the case of TCE, both the parent compound and trichloroethanol, a major metabolite, cause depression of the central nervous system (CNS) when present at sufficient concentrations. PCE can also produce CNS depression. Trichloroacetic acid, a major metabolite of both TCE and PCE, is believed to be primarily responsible for liver tumors in B6C3F$_1$ mice (Bull 2000; Lash et al. 2000a). Thus, it is important to know or to be able to estimate the quantity of the bioactive moiety and how long it remains in the target organ if one wants to predict the magnitude and duration of toxic action (Andersen 1987).

Pharmacokinetics, or toxicokinetics, and physiologically based toxicokinetic (PBTK) models are increasingly important in reducing uncertainties inherent in health risk assessments of TCE, PCE, methylene chloride, and other VOCs (Andersen et al. 1987; Andersen 2003; Clewell and Andersen 2004; Clewell et al. 2005; Krishnan and Johanson 2005). *Toxicokinetics* may be defined as the systemic uptake, distribution, metabolism, interaction with plasma and cellular components, and elimination of toxic chemicals and their metabolites. Kinetic processes determine how much of an external dose is absorbed into the blood; reaches the arterial circulation; binds to plasma proteins or other inactive sites; enters specific organs; is biotransformed to toxicologically active and inactive forms; interacts with target molecules, cells, and tissues; and is eliminated from the target tissue and the body (Bruckner et al. 2008). One or more of those processes can vary widely from one route of exposure to another, from high to low doses, from one species to another, and from one individual to another. Gaining an understanding of how kinetic processes differ can substantially reduce the number of assumptions made in assessing toxicity and cancer risks posed by VOCs.

Volatility and lipophilicity are two of the most important properties of VOCs that govern their toxicokinetics. The volatility of the compounds varies inversely with their molecular weight. TCE, for example, is of lower molecular weight and evaporates more readily than PCE. PCE is more lipid-soluble than TCE. Cell membranes are made up largely of lipids. Halocarbons pass freely through membranes from areas of high to low concentration by passive diffusion.

Absorption

Halocarbons and other VOCs are absorbed through intact human skin to a limited extent. The barrier to penetration is the stratum corneum, the skin's outermost layer. The stratum corneum is composed

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of very tightly adhering, keratinized epithelial cells, which present a much more substantial barrier to halocarbons than do living cell membranes. Important determinants of the rate and extent of percutaneous absorption of a chemical include the integrity and thickness of the stratum corneum, the surface area exposed and duration of contact, and the chemical's concentration, molecular size, and lipophilicity (Stewart and Dodd 1964; EPA 1992). Percutaneous absorption of VOCs is more extensive through rodent than through human skin, owing largely to the rodents' thinner stratum corneum and higher dermal blood flow rate (McDougal et al. 1990; Monteiro-Riviere et al. 1990). Poet et al. (2000) reported that the dermal permeability constant for absorption of 1,1,1,-trichloroethane from water into humans was one-fortieth that into rats. Those researchers concluded that people will not absorb substantial amounts of VOCs through their skin from contaminated water regardless of the duration of exposure. That conclusion conflicts with that of Weisel and Jo (1996) and Gordon et al. (2006), who found percutaneous absorption to be an important route of human exposure.

Halocarbons and most other VOCs are absorbed from the lungs rapidly and extensively. TCE and PCE, for example, appear in the arterial blood of rats within 1 min after initiation of inhalation exposure (Dallas et al. 1991, 1994). Most of the systemic absorption of inhaled VOCs occurs in the alveoli. The small lipophilic molecules readily diffuse bidirectionally through the thin capillary and alveolar type I cells. Such gases in the alveoli are believed to equilibrate almost instantaneously with blood in the pulmonary capillaries (Goldstein et al. 1974). The ratio of the concentration of a VOC in blood to its concentration in air at equilibrium is the blood:air partition coefficient. Partition coefficients have been measured in vitro with human and rat blood for a large number of VOCs (Gargas et al. 1989). Respiratory, or alveolar, ventilation rate and the ratio of cardiac output to pulmonary perfusion rate are two other important determinants of pulmonary uptake of VOCs. VOCs diffuse from areas of high to areas of low concentration, so increases in respiratory rate (to maintain a high alveolar concentration) and increases in pulmonary blood flow rate (to maintain a large concentration gradient by removing capillary blood that contains a VOC) enhance systemic absorption. The higher those factors are, the greater the systemic uptake. The TCE blood:air partition coefficient of the rat is 2.7 times greater than that of the human (Gargas et al. 1989). Resting alveolar ventilation rates of rats and mice are as much as 11 and 23 times higher, respectively, than that of humans. Cardiac outputs of rats and mice are about 6 and 10 times greater than that of humans (Brown et al. 1997). Thus, for equivalent inhalation exposures to TCE and other VOCs, internal doses are substantially higher in rodents than in humans (Bruckner et al. 2008).

Systemic absorption of VOCs during inhalation exposures depends on metabolism and tissue loading, in addition to the factors described above. The percentage uptake of inhaled TCE is initially high in experimental animals. Uptake progressively declines during exposure as a chemical accumulates in tissues, and its concentration in venous blood returning to the lungs increases, reducing the air:blood concentration gradient (Dallas et al. 1989). A near steady state, or equilibrium, in uptake and in blood concentrations is usually reached within an hour and maintained despite continued inhalation of a fixed air concentration of TCE. The same phenomenon was reported recently in human subjects inhaling TCE at 1 ppm for 6 h (Chiu et al. 2007). Blood concentrations of PCE, in contrast, slowly rose in the subjects during the last 4 h of a 6-h exposure to PCE at 1 ppm. That difference is due to PCE's higher lipid solubility, which results in its greater and more prolonged uptake into body fat. Persons using contaminated water at Hadnot Point and Tarawa Terrace probably had intermittent PCE or TCE exposures during the day when they drank water and used heated water. Day-to-day exposures were also intermittent because the individual water-supply wells operated on a cycle schedule (see Chapter 2).

Halocarbons and other VOCs are well absorbed after their ingestion. More than 90% of TCE given in water as an oral bolus (by gavage to rats that have been fasting) is absorbed systemically (D'Souza et al. 1985). Peak blood concentrations are observed within 5-10 min of dosing. The presence of food, particularly fatty foods, in the gut delays absorption of TCE and other organic solvents. Kim et al. (1990a) describe the time course of carbon tetrachloride in the venous blood of rats given an equivalent oral bolus dose of the halocarbon in water and in corn oil. The peak blood concentration of carbon tetrachloride is about 10 times higher in the water-vehicle group than in the oil-vehicle group, but the relationships between blood concentrations of carbon tetrachloride and time in the two groups are essen-

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tially the same. Liver injury is more pronounced in the group that ingested carbon tetrachloride in water, apparently because of the liver's markedly higher exposure to the hepatotoxin during the initial minutes after dosing.

Inhalation results in substantially higher arterial blood and target-organ concentrations of VOCs than does ingestion of comparable doses. A number of factors are responsible for that phenomenon. As described above, fatty foods serve as a reservoir in the gut to prolong the absorption of lipophilic chemicals. All the cardiac output passes through the pulmonary circulation compared with about 20% through the gastrointestinal tract. More rapid blood flow in the lungs creates a greater concentration gradient, which results in more rapid diffusion into the blood. The distance that VOCs must diffuse from their absorption surface to capillaries is considerably shorter in the alveoli than in the gastrointestinal mucosal epithelium. The most important route-dependent difference for well-metabolized VOCs is presystemic elimination after their ingestion (Bruckner et al. 2008).

Presystemic Elimination of Oral Volatile Organic Compounds

A substantial proportion of TCE and other well-metabolized VOCs that are ingested does not reach the arterial circulation or extrahepatic organs. It has not been established whether a significant proportion of low doses of VOCs undergo gastrointestinal metabolic clearance, though researchers have established the presence of several CYP3A isoforms in the small intestines of humans (Obach et al. 2001) and mice and rats (Martignoni et al. 2006). Chemicals absorbed into venous mesenteric blood vessels are conveyed via the portal vein through the liver before entering the mixed venous circulation. The liver contains the highest concentrations of CYP2E1 and other enzymes and is the major site of xenobiotic metabolism in the body. The efficiency of first-pass hepatic metabolism and clearance depends on the administered dose of the chemical, the rate at which it is ingested, and its propensity to be metabolized. White et al. (unpublished data) recently observed that bioavailability of 1,1,1,-trichloroethane, a poorly metabolized halocarbon, was markedly higher in orally dosed rats than was TCE, a well-metabolized halocarbon.[1] The bioavailability of TCE was substantially higher when it was given as a single oral bolus (that is, all at one time) than when it was given slowly over several hours. Administration of the quickly absorbed chemical as a bolus resulted in its rapid arrival in amounts that exceeded (or saturated) the liver's metabolic capacity. In contrast, neither the dose nor the rate of oral administration of 1,1,1,-trichloroethane affected its first-pass hepatic elimination or bioavailability, because it was poorly metabolized. The bioavailability of TCE, however, was significantly lower at lower doses because of its more efficient metabolic clearance. Lee et al. (1996) also found that hepatic first-pass elimination of oral TCE was inversely related to dose in rats. VOCs are exhaled during their first pass through the lungs. Lee et al. (1996) confirmed that pulmonary elimination of TCE was not dose-dependent. Andersen (NRC 1986) had proposed that pulmonary elimination of VOCs was governed instead by a VOC's blood:air partition coefficient. In summary, VOCs that are extensively metabolized and quite volatile are most efficiently eliminated before they reach the arterial circulation.

First-pass, or presystemic elimination, may have major implications for cancer and noncancer risks posed by ingestion of very low concentrations of VOCs in drinking water. Over 25 years ago, Andersen (1981) proposed that the liver was capable of removing "virtually all" of a well-metabolized VOC after its ingestion if the amount in the portal blood was not high enough to saturate hepatic metabolism. As described below, most of the VOCs of interest at Camp Lejeune are extensively metabolized. Metabolism is required for their conversion to potentially cytotoxic or mutagenic substances. The liver should bear the brunt of metabolizing ingested VOCs. However, first-pass hepatic metabolic clearance and exhalation will protect most extrahepatic organs by reducing the amount of parent compounds reaching them.

[1]White, C.A., S. Muralidhara, C. Hines, and J.V. Bruckner. Effect of oral dosage level and rate on the bioavailability and metabolism of trichloroethylene and 1,1,1-trichloroethane. Submitted to Toxicol. Sci. Manuscript being prepared for submission for publication.

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Parent halocarbons, as described previously, can depress CNS functions if they reach the brain in sufficient amounts. A number of extrahepatic tissues—including brain, lung, renal, testicular, and breast tissue and bone marrow—contain CYP2E1, other P-450s, and other enzymes that metabolize xenobiotics (de Waziers et al. 1990; Ding and Kaminsky 2003). The amounts of enzymes are usually considerably lower in those tissues than in the liver but can be high enough in some cell types to form quantities of reactive metabolites adequate to harm the cells. Hepatic halocarbon metabolites stable enough to be transported to other organs can potentially injure those organs. It is widely recognized, for example, that derivatives of glutathione conjugates of TCE and PCE formed in the liver are taken up and metabolized further by the kidneys to substabnces that may be nephrotoxic or carcinogenic (Lash et al. 2000b; Lash and Parker 2001; Lash et al. 2007). VOCs absorbed from the lungs and skin are not subject to presystemic elimination.

The efficiency of presystemic elimination of ingested halocarbons in humans remains to be established. Sufficiently sensitive analytic methods for quantifying VOCs in biologic specimens that allow direct testing of Andersen's (1981) aforementioned hypothesis have not been available until very recently. Lee et al. (1996) used a gas-chromatography-electron-capture headspace technique to measure blood concentrations in assessing presystemic elimination of TCE in rats. Their experimental approach required monitoring complete blood-TCE time courses. The lowest oral dose for which a complete time course could be delineated was 170 μg/kg. Some 60% of the dose was eliminated before reaching the rats' arterial circulation. More recently, a much more sensitive analytic method has been used; it involves VOC extraction and concentration on a solid fiber and measurement with gas chromatography-mass spectrometry. Using that technique, Blount et al. (2006) measured 31 VOCs in the blood of the general U.S. population. Liu et al. (2008) have also used the technique to obtain blood time-course data on rats given TCE orally at as low as 1 ng/kg. Bioavailability was about 10% at the lowest doses. The analytic method's limit of quantification was 25 pg/mL (ppt). Rats have a greater capacity to metabolize TCE and other VOCs than humans, so first-pass hepatic elimination should be somewhat less efficient in humans. Weisel and Jo (1996), however, were able to detect TCE in exhaled breath for only seconds to a few minutes after humans ingested water contaminated with TCE. Chloroform was undetectable in breath samples of persons who consumed chlorinated municipal water; this implies complete first-pass hepatic elimination. The efficiency of human presystemic elimination of TCE and other VOCs at environmental concentrations can be determined by extrapolation from animal data or by direct measurement. In summary, presystemic elimination should protect most extrahepatic tissues from harm after ingestion of TCE, PCE, and other VOCs at environmental concentrations.

Solvent or Vehicle Effects on VOC Toxicity

Oral and dermal administration of VOCs in toxicology studies usually require that the lipophilic chemicals be dissolved or diluted in a suitable solvent. Corn oil and other digestible oils have been the most commonly-used vehicles, though aqueous emulsions, suspensions, and gelatin-encapsulated preparations have been employed in toxicity and carcinogenicity investigations. Considerable effort has been devoted to assessing adverse health effects of VOCs in drinking water. A number of studies have been conducted to determine whether experiments in which VOCs were given to animals in corn oil were relevant to assessing risks from ingestion of VOCs in water. Kim et al. (1990a,b), for example, found that corn oil served as a reservoir in the gut to delay systemic absorption of carbon tetrachloride in rats. Although bioavailability of carbon tetrachloride given in corn oil and in an aqueous Emulphor emulsion was the same, peak blood concentrations of carbon tetrachloride and acute hepatotoxicity were much lower in the corn oil group. Raymond and Plaa (1997) found aqueous preparations of carbon tetrachloride were more acutely hepatotoxic to rats than when it was administered in corn oil, though the converse was true for nephrotoxicity of chloroform. Dissimilar findings have been reported in subacute studies. Condie et al. (1986), for example, observed that carbon tetrachloride was more hepatotoxic to mice after 90 days of oral dosing in corn oil than in an aqueous Tween emulsion. Koporec et al. (1995), however, found no dif-

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ference in rats when given carbon tetrachloride in either corn oil or aqueous solution for 13 weeks. As described below, chloroform and other VOCs have been found to be hepatocarcinogens in mice when given chronically by gavage in corn oil, but not when delivered in drinking water. Under these circumstances, interpretation requires consideration of the confounders introduced by both the vehicle and dose regimen.

There is concern that vehicles may not only affect the absorption of VOCs, but may influence VOC metabolism and disposition and may have biological actions of their own. Oils in the gastrointestinal tract largely retain VOCs until the oil is emulsified and digested (Kim et al. 1990b). The lipids thus delay VOC absorption into the blood and can carry some of the VOC along into the lymphatics. Common surfactants used as emulsifying agents are known to modify drug absorption by altering the physical properties of membranes, as well as certain transport mechanisms (Xia and Onyuksel 2000). Feeding rats a diet supplemented with corn oil enhanced the induction of hepatic cytochrome P4502B1 by phenobarbital (Kim et al. 1990c). This is one isozyme that metabolically activates high doses of TCE and several other VOCs in rats. Feeding animals a high-fat diet containing corn oil increases lipoperoxidation and susceptibility to oxidative stress by reducing antioxidant enzyme defenses (Domitrovic et al. 2006; Slim et al. 1996). A number of investigations have shown increased incidences of breast, colorectal, and prostate cancer in rodents maintained on high-fat diets, but recent human epidemiological studies have largely been inconclusive (Kushi and Giovannucci 2002; Thiebaut et al. 2007; Kobayashi et al. 2008).

Pattern of Water Ingestion

A person's pattern of consumption of VOC-contaminated water can have a marked effect on halogenated chemicals' toxicokinetics and toxic or carcinogenic potential. For convenience in chronic oral-carcinogenicity studies, TCE, PCE, methylene chloride, and chloroform have usually been given daily by gavage. In each instance, an increased incidence of liver tumors in $B6C3F_1$ mice was observed. No such increase was seen when the mice received tumorigenic doses of chloroform and other VOCs in drinking water (Jorgenson et al. 1985; Klaunig et al. 1986). Larson et al. (1994) saw marked necrosis and ensuing proliferation of hepatocytes in $B6C3F_1$ mice given chloroform by gavage, but no such effects in mice that consumed the same daily doses in their water. La et al. (1996) reported greater DNA-adduct formation and hepatocellular proliferation in mice given 1,2,3-trichloropropane by gavage than in those receiving the chemical in drinking water. Sanzgiri et al. (1995) administered the same doses of carbon tetrachloride to rats by gavage and over 2 h by constant gastric infusion. Arterial blood concentrations of carbon tetrachloride and the extent of acute hepatic damage were greater in the gavage groups. Carbon tetrachloride and other halocarbons are quickly absorbed from the gastrointestinal tract, and the rapid delivery of large quantities of carbon tetrachloride to the liver via the portal blood inhibited metabolism and killed hepatocytes. Both effects reduced hepatic metabolic clearance of the chemical. Such findings raise questions about the relevance of gavage toxicity and cancer-study results to real-life human exposures, in which people typically ingest contaminated water in divided doses over the course of the day.

Systemic Distribution

VOCs are transported by the arterial blood to tissues throughout the body. The lipophilic compounds do not bind appreciably to plasma proteins or hemoglobin but partition into their hydrophobic regions and into phospholipids, lipoproteins, and cholesterol present in the blood (Lam et al. 1990). Initial uptake into tissues depends primarily on their rate of blood flow and tissue:blood partition coefficient. The brain is a prime example of an organ with a high perfusion rate and high lipid content, hence a high brain:blood partition coefficient. Lipophilic VOCs quickly accumulate in the brain and can rapidly depress its functions on initiation of sufficiently high external exposures (Warren et al. 2000). Inhalation of a few hundred ppm of TCE and PCE can inhibit psychophysiological functions in humans, while inhala-

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tion of several thousand ppm will rapidly produce marked CNS depression. Then, redistribution to poorly perfused lipid-rich tissues (such as bone marrow, skin, and fat) with even higher tissue:blood partition coefficients occurs. Adipose tissue gradually accumulates large amounts of VOCs and slowly releases them back into the bloodstream because of its high tissue:blood partition coefficient and low blood perfusion rate. That prolongs exposure of other tissues to the chemicals (Bruckner et al. 2008).

Metabolic Activation and Inactivation of Trichloroethylene and Perchloroethylene

Metabolism, or biotransformation, plays a key role in modulating the toxicokinetics and the ensuing toxicity or carcinogenicity potential of the VOCs of interest at Camp Lejeune. As described previously, most VOC metabolism occurs in the liver. Biotransformation in other tissues is quantitatively insignificant but can be toxicologically significant if CYP2E1 and some other enzymes are present. Specific hepatic and extrahepatic enzymes convert the VOCs to relatively water-soluble metabolites that can be eliminated more readily in the largely aqueous urine and bile. Conversion of the parent compounds and their reactive metabolites to less active or inactive metabolites that are more water-soluble and therefore more efficiently eliminated is termed metabolic inactivation or detoxification. The relative extent of activation and inactivation of VOCs can vary substantially from one species to another and from one individual to another. It is well established that the metabolic activation of the VOCs of interest in Camp Lejeune water, in decreasing order of magnitude, is as follows: mice > rats > humans (Elfarra et al. 1998; Lipscomb et al. 1998; Volkel et al. 1998; Lash and Parker 2001). Mice express very low concentrations of epoxide hydrolase (Lorenz et al. 1984), the enzyme that catalyzes the hydrolytic degradation (detoxification) of highly reactive epoxide metabolites of TCE and PCE. Many other factors or variables may also influence the metabolism and toxicokinetics of VOCs (Lof and Johanson 1998).

The metabolic activation and inactivation of TCE has been described in detail elsewhere (ATSDR 1997b; Lash et al. 2000a; NRC 2006). TCE is metabolized primarily via an oxidative pathway involving sequential formation of a series of metabolites. The second, relatively minor pathway involves glutathione (GST) conjugation (Figure 3-2). The key metabolic pathways and metabolites of toxicologic interest are described briefly below.

The initial step in the oxidative pathway is catalyzed by microsomal cytochrome P-450s. CYP2E1, as noted previously, is the primary P-450 isozyme responsible for oxidation of low concentrations of TCE (Lipscomb et al. 1997; Ramdhan et al. 2008). P-450-catalyzed oxidation of TCE in rodents and humans, in decreasing order of magnitude, is as follows: mice>rats>humans (Lash et al. 2000a). Whether TCE is initially converted to TCE oxide is controversial. Cai and Guengerich (2001) were able to detect formation of trace amounts of the epoxide by phenobarbital-induced rat liver P-450s but not by human liver P-450s. The majority of TCE is apparently converted to an oxygenated TCE-P-450 intermediate, which rearranges to form chloral, a major metabolic intermediate. Chloral is oxidized to chloral hydrate, a sedative widely used in medical and dental procedures in infants and children (Vade et al. 1995; Keengwe et al. 1999). Chloral hydrate is both oxidized to trichloroacetic acid and reduced to trichloroethanol. Much trichloroethanol is conjugated with glucuronic acid and excreted in the urine. Trichloroethanol glucuronide that is excreted in the bile is hydrolyzed, reabsorbed, and oxidized in part to trichloroacetic acid. Chiu et al. (2007) recently observed that concentrations of trichloroacetic acid were significantly lower than trichlorethanol and trichloroethanol glucuronide concentrations in the blood of humans who had inhaled TCE at 1 ppm for 6 h. Modest amounts of dichloroacetic acid apparently are produced from trichloroacetic acid and trichloroethanol in mice, but relatively little dichloroacetic acid is formed in rats. Trace amounts of dichloroacetic acid were detected in one study of TCE-exposed humans (Fisher et al. 1998) but not in other studies (Lash et al. 2000b; Bloemen et al. 2001). Both trichloroacetic acid and dichloroacetic acid have been shown to be hepatic carcinogens in mice at high doses (Bull 2000). It is generally accepted that trichloroacetic acid is a nongenotoxic liver carcinogen in $B6C3F_1$ mice, although its ability to cause liver cancer in humans has been discounted by findings in a number of labo-

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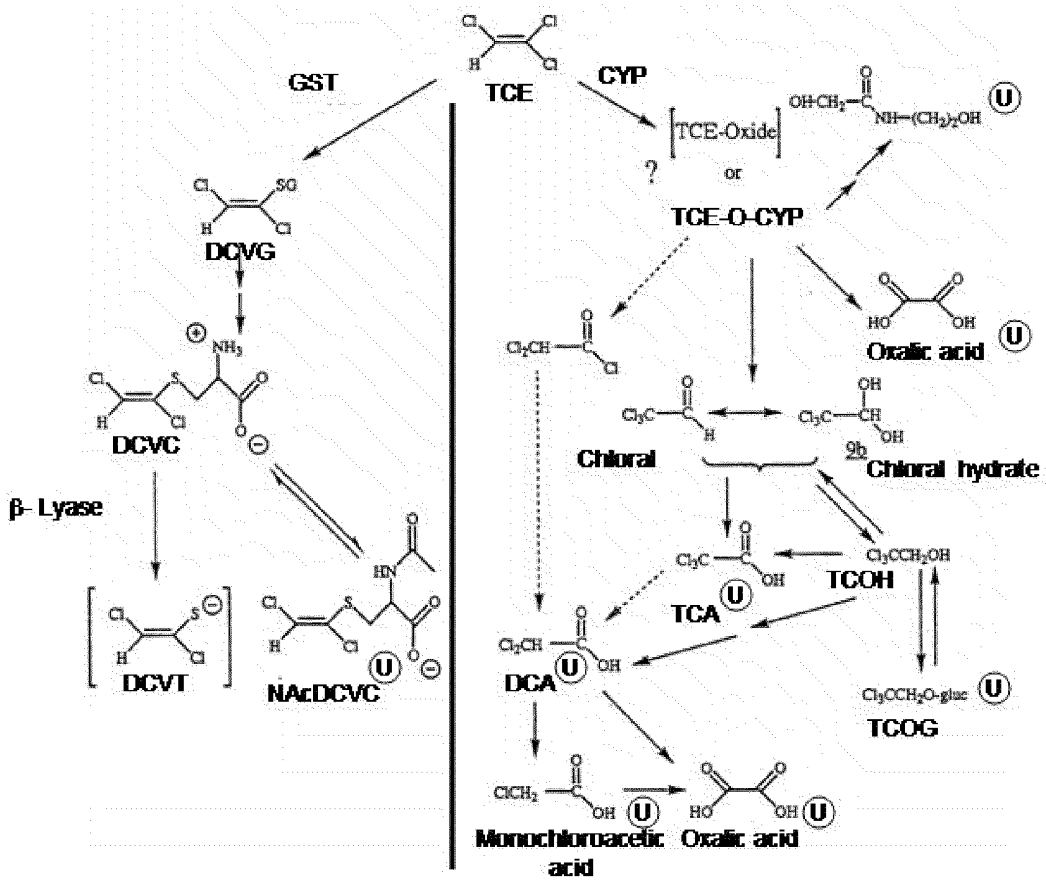


FIGURE 3-2 Metabolism of trichloroethylene. Metabolites marked with Ⓤ are known urinary metabolites. Arrows with broken lines indicate other possible steps in forming DCA. CYP, cytochrome P-450; DCA, dichloroacetic acid; DCVC, *S*-(1,2-dichlorovinyl)-L-cysteine; DCVG, *S*-(1,2-dichlorovinyl)glutathione; DCVT, *S*-(1,2-dichlorovinyl)thiol; GST, glutathione *S*-transferase; NAcDCVC, *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine; TCA, trichloroacetic acid; TCE, trichloroethylene; TCE-O-CYP, trichloroethylene-oxide-cytochrome P-450 complex; TCOG, trichloroethanol glucuronide; TCOH, trichloroethanol. Source: NRC 2006.

ratory investigations (Bull 2000; Moore and Harrington-Brock 2000). The possible causative role of dichloroacetic acid in human liver cancer is even more controversial (Walgren et al. 2005; Caldwell and Keshava 2006; Keshava and Caldwell 2006; Klaunig et al. 2007).

The glutathione conjugation pathway is quite similar qualitatively, but not quantitatively, in rats and humans. The initial step in this second, minor pathway involves conjugation of TCE with glutathione to form *S*-(1,2-dichlorovinyl)glutathione (DCVG). DCVG formation occurs primarily in the liver at a rate about 10 times greater in rats than in humans (Green et al. 1997a). Much of the DCVG is excreted via the bile into the intestines and converted to *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC). That metabolite is reabsorbed and taken up by the liver, where a portion is detoxified by *N*-acetylation. Bernauer et al. (1996) exposed rats and humans to TCE vapor at up to 160 ppm for 6 h. The rats excreted 8 times more *N*-acetyl-DCVC in their urine than did the human volunteers at each exposure level. Some DCVC is taken up by the kidneys and further metabolized by the enzyme β-lyase to *S*-(1,2-dichlorovinyl)thiol (DCVSH). DCVSH is then converted to unstable, highly reactive products, including chlorothioketene and thionoacylchloride (Lash et al. 2000a). Metabolic activation of DCVC to chlorothioketene was shown to occur 11 times more rapidly in rats than in humans (Green et al. 1997a). Lash et al. (2001b) also demonstrated that cultured rat renal cells are more sensitive to DCVC than are human renal cells. Chlorothioketene and

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similarly unstable congeners are capable of covalently binding to renal cellular proteins and DNA, and this results in genotoxicity and cytotoxicity with ensuing regenerative hyperplasia and potentially renal-cell carcinoma.

PCE, like TCE, is metabolized through cytochrome P-450-catalyzed oxidation and glutathione conjugation (Figures 3-3 and 3-4). CYP2E1 is not thought to play a major role. PCE is believed to be oxidized primarily by the CYP2B family in the rat (Hanioka et al. 1995). In humans, CYP2B6 is the primary isoform responsible for PCE metabolism, and there are minor contributions by CYP1A1 and CYP2C8 (White et al. 2001). The initial metabolite is the epoxide PCE-oxide. That metabolic intermediate can be biotransformed to several products (Lash and Parker 2001). The primary one is trichloroacetyl chloride, which reacts with water to form trichloroacetic acid, the predominant PCE metabolite found in the urine of rodents and humans (Birner et al. 1996; Volkel et al. 1998). Some trichloroacetic acid is converted to dichloroacetic acid. PCE is a much poorer substrate for CYPs than TCE (that is, PCE is much less

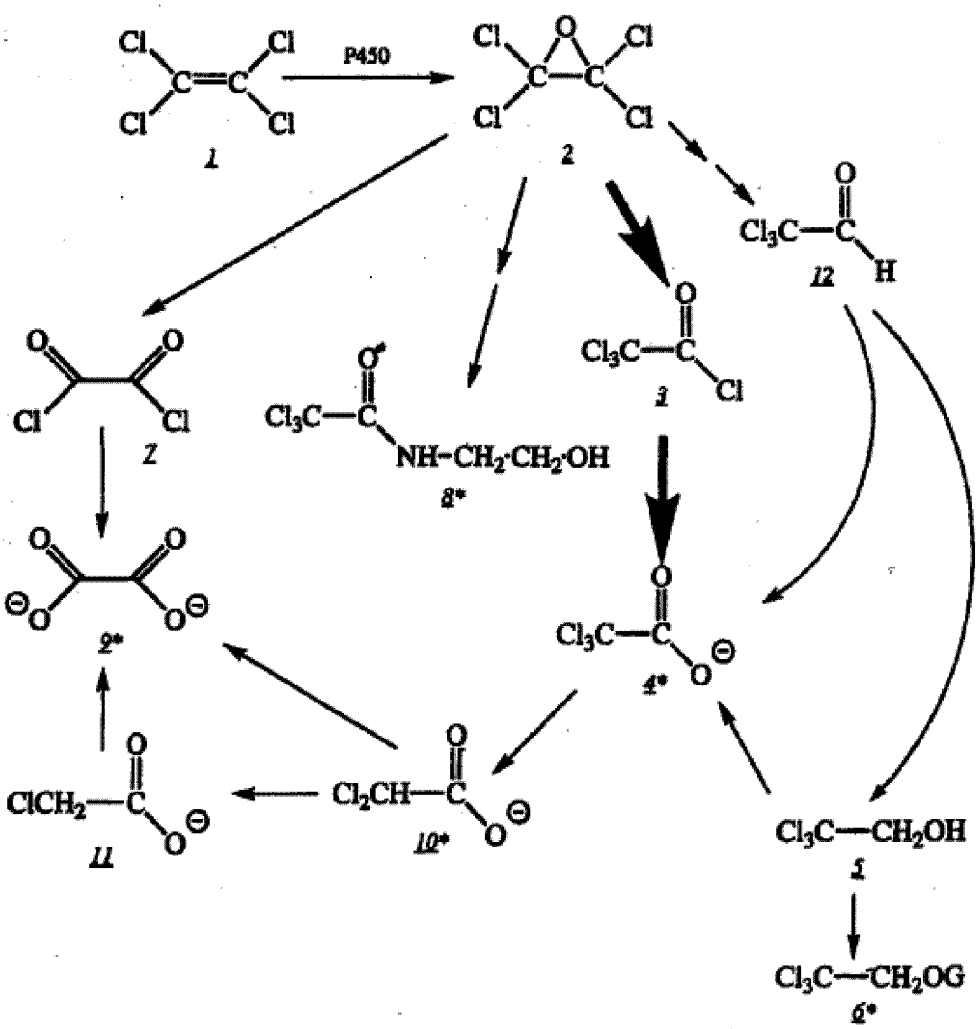


FIGURE 3-3 Metabolism of PCE by P-450 pathway. *Identified urinary metabolites: 1, PCE; 2, PCE epoxide; 3, trichloroacetyl chloride; 4, trichloroacetate; 5, trichloroethanol; 6, trichloethanol glucuronide; 7, oxalate dichloride; 8, trichloroacetyl aminoethanol; 9, oxalate; 10, dichloroacetate; 11, monochloroacetate; 12, chloral. Source: Lash and Parker 2001. Reprinted with permission; copyright 2001, *Pharmacological Reviews*.

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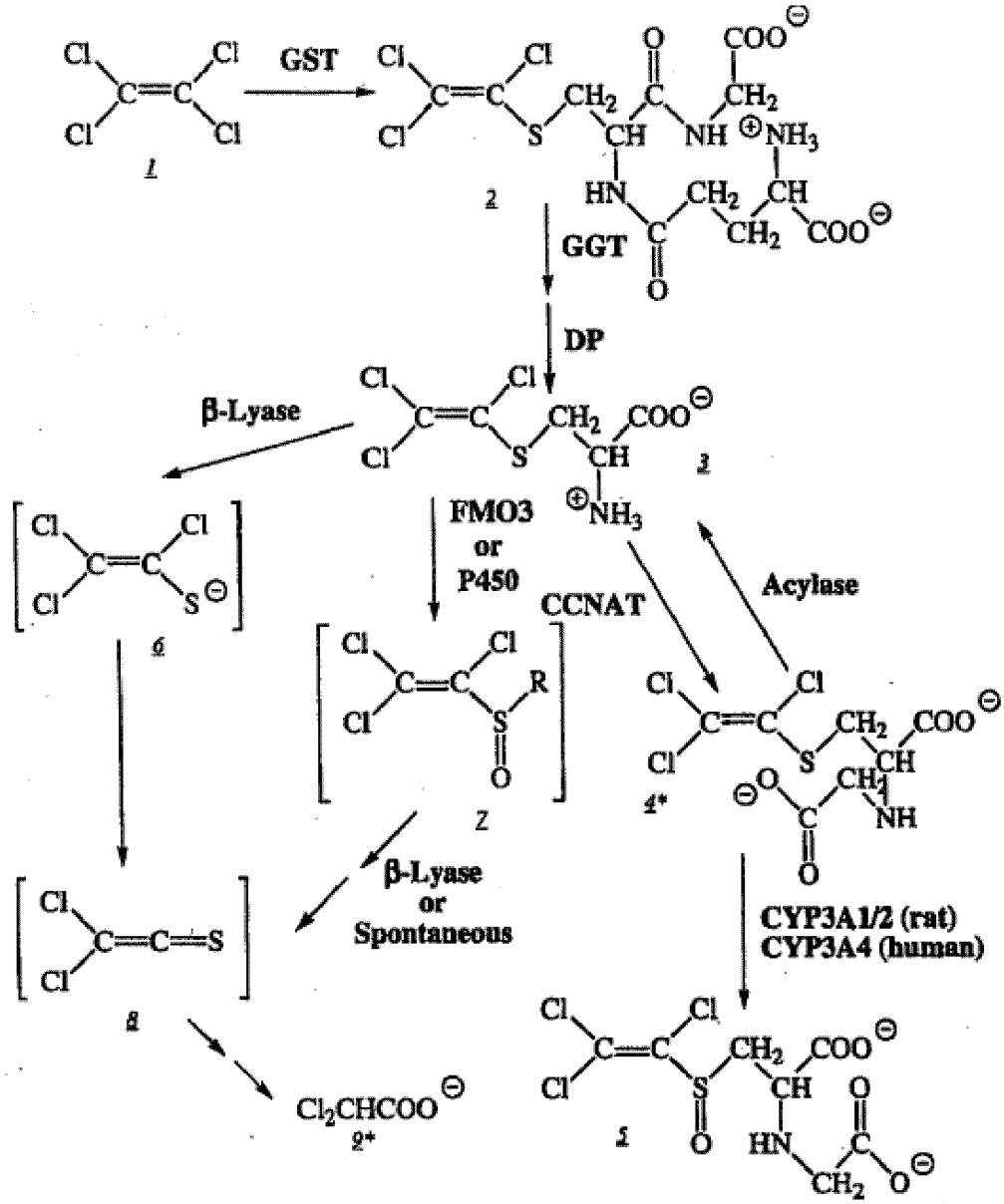


FIGURE 3-4 Metabolism of PCE by glutathione conjugation pathway. *Identified urinary metabolites: 1, PCE; 2, TCVG; 3, TCVC; 4, NAcTCVC; 5, NAcTCVC sulfoxide; 6, 1,2,2-trichlorovinylthiol; 7, TCVCSO; 8, 2,2-dichlorothioketene; 9, dichloroacetate. Enzymes: GST, GGT, dipeptidase (DP), β-lyase, FMO3, CCNAT, CYP3A1/2, and CYP3A4. Unstable, reactive metabolites are shown in brackets. Source: Lash and Parker 2001. Reprinted with permission; copyright 2001, *Pharmacological Reviews*.

extensively metabolized than TCE) (ATSDR 1997c; Chiu et al. 2007). Saturation of PCE oxidative metabolism occurs at a lower exposure concentration in humans than in rats. Rats metabolize substantially more PCE to trichloroacetic acid than do humans (Volkel et al. 1998). Only traces of dichloroacetic acid were detected in the urine of persons who inhaled PCE at 40 ppm for 6 h. Rats subjected to an equivalent exposure excreted relatively large amounts of dichloroacetic acid, a rodent hepatic carcinogen.

A small proportion of absorbed PCE undergoes conjugation with glutathione to form *S*-(1,2,2-trichlorovinyl) glutathione (TCVG). That initial metabolic step is catalyzed by glutathione *S*-transferases

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and occurs primarily in the liver. TCVG is converted to *S*-(1,2,2-trichlorovinyl)-L-cysteine (TCVC). TCVC, like the DCVC formed from TCE, is both detoxified in the liver by *N*-acetylation and metabolically activated by β-lyase in the kidneys to cytotoxic, mutagenic thioketenes (Lash and Parker 2001). TCVC is also oxidized by flavin-containing monooxygenase 3 (FMO3) to TCVC sulfoxide (Ripp et al. 1997), which can rearrange spontaneously to form 2,2-dichlorothioketene. Thus, potent alkylating agents are formed via two subpathways in the kidneys. 2,2-Dichlorothioketene can also decompose to dichloroacetic acid. Hence, dichloroacetic acid is derived from both glutathione- and CYP-dependent biotransformation of PCE. PCE is conjugated with glutathione more extensively by rats (1-2% of the dose) (Dekant et al. 1986) than is TCE (less than 0.005% of the dose) (Green et al. 1997a). The extent of glutathione conjugation of PCE increases when the oxidative pathways begin to become saturated at high PCE exposure concentrations. Metabolic products of glutathione conjugates of TCE and PCE are primary contributors to the halocarbons' nephrotoxicity (Lash et al. 2007).

Humans are likely to be less susceptible than rodents to the toxic or carcinogenic actions of PCE, as they are to those of TCE. Humans absorb less inhaled PCE and TCE, attain lower target-organ doses, and metabolically activate a smaller proportion of their internal dose. As noted above, rats exhibit a higher capacity for oxidation of PCE. Volkel et al. (1998) report finding substantially higher urinary excretion of trichloroacetic acid, *N*-acetyl TCVC, and dichloroacetic acid in the urine of rats than in the urine of humans subjected to identical PCE inhalation regimens. Lash et al. (1990) and Cooper (1994) report 10 times higher activity of cysteine conjugate β-lyase activity in rat than in human kidney. Green et al. (1990) report that β-lyase-dependent metabolism of TCVC in rat kidney cystosol is more rapid and efficient than in either mice or humans. TCVC metabolism is also greater in male than in female rats. The male rat is more susceptible to PCE-induced nephrotoxicity. A low incidence of kidney cancer is seen in male but not female rats in TCE and PCE cancer bioassays (ATSDR 1997b,c).

It is evident from the foregoing there is a great deal of information about the toxicokinetics, metabolism, and toxicology of TCE, PCE, and other VOCs in laboratory animals and humans. That knowledge allows scientists to judge the relevance of VOCs' adverse effects in animals to humans with a reasonable degree of certainty. Mice and rats absorb more inhaled TCE and PCE, metabolically activate more of their absorbed dose, and inactivate epoxide metabolites less efficiently than do humans. Such interspecies toxicokinetic differences contribute to the greater susceptibility of rodents than of humans to TCE- and PCE-induced hepatic, lung, and renal tumors. Toxicodynamic species differences that predispose $B6C3F_1$ mice to liver cancer are also recognized (see Chapter 4).

POTENTIALLY SENSITIVE POPULATIONS

Many factors or variables may alter the toxicokinetics of and the responses of a person to TCE, PCE, and other VOCs (Lof and Johanson 1998; Bruckner et al. 2008). Some variables that are characteristic of a particular group may increase susceptibility, others reduce it, and still others have no influence. The net effect of circumstances involving multiple variables can be difficult to predict. There are scenarios in which the toxicity or carcinogenicity of moderate exposure (for example, occupational exposure) or high exposure (for example, in animal cancer studies) to some VOCs may be significantly affected by variables like age, sex, genetics, physiologic condition, or lifestyle. As discussed below, that appears not to be the case for the concentrations of most of the VOC contaminants identified in water at Camp Lejeune.

Children

There is concern that infants and children may be more vulnerable than adults to some adverse effects of chemicals (Dourson et al. 2002; Daston et al. 2004). A National Research Council report (NRC 1993) emphasized that there were "windows of vulnerability" or short periods of early human develop-

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ment when chemical exposures may significantly alter organ function or structure. Potentially vulnerable targets in infants and young children include the endocrine, reproductive, immune, visual, and nervous systems. Little information is available on the effects of TCE, PCE, and other solvents on the development of those organ systems in laboratory animals or humans. There is considerably more knowledge of consequences of exposure of adults, as discussed in Chapter 4.

It is not clear whether organ-system development of young children or animals is influenced by exposure to VOCs. A number of chemicals—such as lead, mercury, thalidomide, chloramphenicol, and organophosphorus insecticides—are known to have more pronounced adverse effects in infants and young children than in adults (Bruckner 2000). Children are not necessarily more susceptible to toxicants. The most definitive human data on age-dependence available to the 1993 National Research Council committee were maximum tolerated doses of a variety of anticancer agents. Clinical trials in pediatric and adult patients revealed that children could tolerate higher doses of most of the antitumor drugs (Glaubiger et al. 1982; Marsoni et al. 1985). Susceptibility can vary markedly with a child's age. The youngest (premature and full-term newborns) are generally the most sensitive to drugs and other chemicals.

Toxicodynamic and toxicokinetic factors are responsible for age-dependent differences in the toxicity of VOCs and other chemicals. Toxicokinetic processes determine the amount of the active form of a chemical that reaches its target tissue or cell and how long it remains there. *Toxicodynamics* refers to the sequence of events that occur in a target tissue or cell on arrival of the bioactive form of a chemical. The events culminate in adverse effects that, in turn, dictate the magnitude and duration of toxic action. Major anatomic, biochemical, and physiologic changes occur during the neonatal period, infancy, childhood, and adolescence. Maturation can markedly affect the absorption, distribution, metabolism, and elimination of many chemicals (Bruckner and Weil 1999; Bruckner 2000; Ginsberg et al. 2004).

The systemic absorption of VOCs may be somewhat higher in infants in connection with some routes of exposure. Infants' and young children's respiratory rates and cardiac outputs are relatively high and favor uptake of inhaled VOCs. That is counteracted to some extent by their smaller alveolar surface area for absorption (Snodgrass 1992). The rate of dermal absorption is comparable in full-term newborns and adults, although the ratio of skin surface area to body weight is about 2.7 times greater in infants than in adults. TCE, PCE, and other solvents are well absorbed from the gastrointestinal tract of all age groups. The low plasma binding capacity of neonates should result in an increased rate of excretion of dichloroacetic acid and trichloroacetic acid, carcinogenic metabolites of TCE and PCE in mice, but it may be offset by neonates' larger extracellular water content, from which the metabolites have to be cleared. The net effect of immaturity on toxicokinetics can be quite difficult to predict (Bruckner 2000; Pastino et al. 2000).

Age-dependent changes in biotransformation have been reasonably well characterized in humans and may have the greatest impact on VOC toxicokinetics and health risks (Hines and McCarver 2002). Concentrations of metabolic enzymes are quite low in newborns and develop asynchronously during the initial months and years. Concentrations of CYP2E1, the P-450 isozyme primarily responsible for oxidation of low doses of TCE (Guengerich et al. 1991), are very low at birth and increase steadily during the first year of life (Johnsrud et al. 2003). Because infants lack the enzymes that convert TCE, PCE, and other VOCs to toxic or mutagenic metabolites, they should be less susceptible to the chemicals than adults. Concentrations of CYP2E1 and additional enzymes that catalyze other steps in VOC metabolic pathways generally attain adult values within 6 months to 3 years. Reimche et al. (1989) determined the half-lives of chloral hydrate, an obligate oxidative metabolite of TCE, in premature newborns, full-term newborns, and young children to be 39.8, 27.8, and 9.7 h, respectively. That finding shows how the ability to eliminate chloral hydrate metabolically increases with maturity. The greater metabolic clearance in children 1-6 years old is apparently due to their larger liver volume and higher blood flow (Murry et al. 2000) rather than higher CYP2E1 activity (Blanco et al. 2000). Greater metabolic capacity may result in increased formation of reactive metabolites of TCE and PCE, although they should also be more rapidly eliminated. Xenobiotic metabolism is similar in older children, adolescents, and adults (Alcorn and McNamara 2002).

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Age-related changes in one toxicokinetic process may be offset or augmented by concurrent changes in other processes. Validated PBTK models are useful for predicting target-organ doses of biologically active parent compounds or metabolites under such circumstances. Sarangapani et al. (2003) constructed a PBTK model that integrated age-specific respiratory measures so that the disposition of four VOCs (PCE, vinyl chloride, isopropanol, and styrene) could be predicted; blood concentrations of the parent compounds in infants and adults were comparable or differed by a factor of less than 2 during the first year of life. Nong et al. (2006) recently incorporated age-specific liver volumes and CYP2E1 content into a PBTK model for toluene; combined interindividual and interage variability in blood toluene concentrations over the periods of monitoring were within a factor of 2 except in neonates, whose concentrations were higher. Clewell et al. (2004) developed a "life-stage model" to simulate blood concentrations of VOCs (PCE, methylene chloride, vinyl chloride, and isopropanol); the predicted internal concentrations at different life stages were within a factor of 2 except during the neonatal period, when the largest differences were manifested. A recent model by Rodriguez et al. (2007) similarly yielded predictions of relatively high blood concentrations of TCE, PCE, methylene chloride, benzene, chloroform, and methyl ethyl ketone in neonatal rats; the increases were due largely to pronounced metabolic immaturity in neonates.

In summary, there is cause for concern that infants and young children will be more susceptible to adverse effects of chemicals. Anatomic and physiologic immaturity can predispose younger people to higher target-organ concentrations of some classes of chemicals. Heavy metals, such as lead and mercury, are known to be absorbed from the gastrointestinal tract and deposited in the brain in greater quantities in infants and young children. Cells in some developing organs (such as neurons in the brain) are more sensitive to injury because they must undergo highly ordered division, differentiation, and migration to function effectively in later life; relatively low concentrations of lead inhibit those processes and affect neurodevelopment and cognitive ability. Conversely, clinical experience has shown that children tolerate higher doses of a number of anticancer drugs than do adults before exhibiting toxicity. Thus, susceptibility is both chemical-dependent and age-dependent. The youngest (premature and newborn infants) are usually the most different from adults and the most likely to be more sensitive to chemical injury. The net effect of anatomic and physiologic immaturity on sensitivity is difficult to predict for chemicals on which there have been few or no studies or data. Although few data are available for TCE, PCE, and other VOCs, PBTK models predict a difference of no more than a factor of 2 in blood concentrations of VOCs after equivalent exposures of infants and adults. Newborns are predicted to have the highest blood concentrations and would be expected to be the most sensitive to any neurologic effects caused by high doses of the parent compounds. Newborns should be less susceptible to adverse effects caused by metabolites formed from lower doses of VOCs due to their immature xenobiotic metabolic systems.

The Elderly

The elderly, like infants and children, may be more or less susceptible than young adults to VOC toxicity. The net effect of pharmacodynamic and pharmacokinetic changes with aging determines the sensitivity of geriatric populations. The aging CNS, for example, undergoes pharmacodynamic changes (such as neuronal loss, alteration in neurotransmitter and receptor numbers, and reduction in adaptability to effects of toxicants) that may predispose to neurotoxicity (Ginsberg et al. 2005). Kiesswetter et al. (1997) observed more pronounced neurobehavioral effects of single or mixed solvents in occupational settings in older workers. Data are sorely lacking, however, on susceptibility to most other adverse effects.

Toxicokinetic changes during aging have been of interest primarily with respect to therapeutics, although the environmental-health arena is now also focusing attention on geriatric populations (Geller and Zenick 2005). Despite some reduction in pulmonary capacity, inhalation PBTK-model predictions of steady-state blood concentrations of PCE, vinyl chloride, styrene, and isopropanol differ little among 10-, 15-, 25-, 50-, and 75-year-old people (Sarangapani et al. 2003). Systemic clearance of many drugs is typically slower after the age of 60 years, particularly in those more than 80 years old (Ginsberg et al. 2005).

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Slowing of clearance is due largely to diminution in cardiac output, which in turn reduces hepatic blood flow and metabolism and renal blood flow and excretion (McLean and LeCouteur 2004). Clewell et al. (2004) predicted that, for a given magnitude of exposure, blood concentrations of PCE and trichloroacetic acid, its major metabolite, would progressively rise during old age. That was attributed to reduction in pulmonary and metabolic clearance of PCE coupled with its accumulation in relatively large amounts of adipose tissue. Much work remains to be done to refine geriatric PBTK models and to integrate them with age-dependent pharmacodynamic changes.

There are sources of variability other than pharmacodynamic and pharmacokinetic changes in responses of geriatric populations to chemicals. They include the common use of multiple medications, inadequate nutrition, and the prevalence of pre-existing disease states (Schmucker 1985). Compromised organ function can be exacerbated by toxicants in such a way that a modest degree of damage may result in marked dysfunction. In addition, normal aging processes can be accentuated by chemical stressors.

Sex Differences

It does not appear that women will differ substantially from men in most respects in their responses to TCE and most other VOCs. Uptake and disposition of these lipophilic chemicals, however, can differ because of the higher proportion of body fat in many females. Absorbed doses of inhaled VOCs are usually higher and internal exposure longer in females. Nomiyama and Nomiyama (1974), for example, measured lower TCE concentrations in the exhaled breath of women volunteers after controlled inhalation exposure. Clewell et al. (2004) used a PBTK model to simulate concentrations of PCE and trichloroacetic acid in men and women over a lifetime of daily ingestion of PCE at 1 μg/kg. The women were predicted to attain higher blood PCE and trichloroacetic acid concentrations. The major sex differences in cytochrome P-450-mediated hepatic metabolism and drug kinetics observed in rats have not been found in humans and other mammals (Schwartz 2003; Bebia et al. 2004). Sex-specific biotransformation data are lacking, however, on most VOCs. Activity of CYP2E1, the major catalyst of oxidation of low concentrations of many VOCs, does not differ significantly between men and women (Snawder and Lipscomb 2000). Nevertheless, a sex-specific PBTK model predicts that women will exhibit higher blood benzene concentrations and 23-26% higher benzene metabolism, which might place them at greater risk than men after equivalent exposures (Brown et al. 1998); higher female body fat content was the major factor in this instance. Another PBTK model's predictions of steady-state blood concentrations of PCE, vinyl chloride, and styrene were largely sex-independent (Sarangapani et al. 2003). Relatively little is known about potential influences of contraceptives or hormone-replacement therapy on the metabolism and disposition of chemicals.

Pregnancy

Relatively little is known about the potential influence of pregnancy on the absorption, distribution, metabolism, and elimination of VOCs. Physiologic changes that occur during pregnancy may protect against or enhance vulnerability to xenobiotic toxicity. Physiologic changes in gastrointestinal, cardiovascular, pulmonary, and renal systems may also affect xenobiotic absorption and elimination (Mattison et al. 1991). Fisher et al. (1989) developed a PBTK model for TCE and its primary metabolite, trichloroacetic acid, in the pregnant rat. Pregnant rats were exposed to TCE by inhalation, as a single oral bolus, or in drinking water. The PBTK model predicted that fetal exposure to TCE and TCA would be over 60% of the maternal exposure regardless of the exposure route. The results suggested that a developing fetus is at risk of TCE and TCA exposure, but such modeling has not been completed for humans.

Biochemical changes during pregnancy may also influence xenobiotic metabolism. Placental and fetal tissues, termed the fetoplacental unit, contain a variety of cytochrome P-450s, the enzyme superfamily responsible for much of phase I xenobiotic metabolism (Raucy and Carpenter 1993; Pasanen and

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Pelkonen 1994). Nakajima et al. (1992) found decreased cytochrome P-450 concentrations in the liver of pregnant Wistar rats. Pregnancy also decreased the metabolism of both TCE and toluene by maternal hepatic microsomes. Active CYP2E1 is believed to be present in human placenta at very low or negligible concentrations, although some evidence suggests that placental CYP2E1 may be induced by high exposure to ethanol (Rasheed et al. 1997; Hakkola et al. 1996; Botto et al. 1994). In general, those findings imply that the mother and fetus would be less exposed to the toxic metabolites formed via the oxidative metabolic pathway. Conversely, they would be more exposed to the parent compound. Because the placenta has little CYP2E1 activity, some amount of oxidative metabolites could be released into fetal circulation.

It is not clear whether CYP2E1 is present in the human fetus. Vieira et al. (1996) found no evidence of human fetal hepatic CYP2E1 before birth, although concentrations of the isozyme rapidly increase after birth. In contrast, Carpenter et al. (1996) detected CYP2E1 in human fetal liver during weeks 16-24 of gestation. In addition, CYP2E1 protein concentrations increased in human fetal hepatocytes exposed to ethanol or clofibrate.

There is no evidence of CYP2B6 mRNA expression or protein in the fetoplacental unit during any stage of pregnancy. Nonetheless, CYP2B6 is believed to be active in the oxidative metabolism of high doses of TCE, PCE, and other VOCs. Further study is needed to clarify those discrepancies in the presence and activity of fetoplacental CYP2E1 and CYP2B6.

A new subject of research is the effect of pregnancy on peroxisome-proliferator-activated receptors (PPAR). PPARs are transcription factors that belong to the nuclear hormone receptor superfamily. PPARs regulate genes involved in cell differentiation, development, and metabolism. The three identified and described PPAR isoforms are PPARα, PPARβ/δ, and PPARγ. Among the isoforms, PPARγ has the greatest influence on cellular homeostasis and carcinogenicity. However, all three PPAR isoforms play essential roles in physiologic change and development in the fetoplacental unit. Abnormalities in PPAR-regulated pathways may be implicated in reproductive and gestational disease (Toth et al. 2007; Borel et al. 2008). Two TCE metabolites, TCA and DCA, can induce PPARα activation in humans. The combined effect of pregnancy and TCE-metabolite-induced PPAR activation is unknown.

Genetics

A variety of genetic polymorphisms can affect the quantity and quality of enzymes and the outcomes of exposure to solvents (Raunio et al. 1995; Wormhoudt et al. 1999). Such polymorphisms occur with different frequencies in different ethnic groups. It is often difficult to disentangle the influence of genetic traits from those of lifestyle and socioeconomic status. Shimada et al. (1994) report that Caucasians have higher total cytochrome P-450 and CYP2E1 concentrations than Japanese. Stephens et al. (1994) describe ethnic differences in the CYP2E1 gene among American blacks, European-Americans, and Taiwanese. Pronounced interethnic differences in rates of ethanol metabolism are associated with alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms. Alcohol dehydrogenase and aldehyde dehydrogenase catalyze secondary reactions in the TCE oxidative pathway. Inasmuch as CYP2E1 catalyzes the bioactivation of a number of VOCs to cytotoxic or mutagenic products (Guengerich et al. 1991), substantial differences in CYP2E1 concentrations in groups might be expected to result in different susceptibilities to injury. Lipscomb et al. (1997) found that hepatic CYP2E1 activity varied by a factor of about 10 in humans. PBTK model simulations of an 8-h inhalation exposure to TCE at 50 ppm and of consumption of 2 L of water containing TCE at 5 ppb revealed that the amount of VOC oxidized in the liver differed by only 2% in persons with the lowest and highest CYP2E1 content (Lipscomb et al. 2003). That blood delivery of TCE to the liver is much slower than CYP2E1-mediated bioactivation limits the influence of individual variability in CYP2E1. That phenomenon is addressed again below in connection with ethanol induction of TCE metabolism. Results of epidemiologic studies of possible relationships between CYP2E1 concentrations and cancer incidence in VOC-exposed groups have been contradictory, and studies of larger populations and having greater statistical power are needed.

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Other polymorphisms have been examined for their possible role in tumor induction in solvent-exposed populations. Bruning et al. (1997), for example, investigated the prevalence of glutathione *S*-transferase (GST) isozyme polymorphisms in TCE-exposed workers who had renal-cell carcinoma. The glutathione conjugation pathway appears to be responsible for formation of cytotoxic or genotoxic metabolites of TCE and PCE (see earlier section "Metabolic Activation and Inactivation of Trichloroethylene and Perchloroethylene"). Bruning et al. (1997) noted that workers who had renal-cell carcinoma were more likely to carry functional GST1 and GSTM1 genes. High percentages of Caucasians and other ethnic groups lack GSTM1 and GSTT1 (Bolt and Their 2006) and thus might be at reduced risk of renal cell carcinoma from TCE or PCE (Vermeulen and Bladeren 2001). Wiesenhutter et al. (2007), however, found no evidence that GSTM1, GSTP1, or NAT2 deletion polymorphisms affected development of renal cell carcinoma in persons with high occupational exposure to TCE.

In conclusion, genetic differences in metabolic activation of TCE by the oxidative pathway do not appear likely to influence toxic or carcinogenic risks posed by the chemical at the concentrations measured in mixed water supplies at Camp Lejeune. Polymorphisms that dictate the presence or absence of genes that code for isozymes that initiate metabolic activation of TCE via the glutathione conjugation pathway are more likely to influence susceptibility to TCE-induced kidney cancer.

Lifestyle

Dietary habits can influence the absorption, metabolism, and toxicity of VOCs in several ways. VOCs are rapidly absorbed by passive diffusion from all parts of the gastrointestinal tract. On ingestion with dietary fat, the chemicals partition into the lipids, and they remain there until they are emulsified and absorbed. That delays systemic uptake of VOCs, such as carbon tetrachloride, and results in reduced blood concentrations and reduced hepatic damage in rats (Kim et al. 1990a, b). Conversely, consumption of a high-fat diet increases hepatic CYP2E1 activity in rats, which can enhance the bioactivation of carbon tetrachloride and other VOCs (Raucy et al. 1991). Carbohydrate deficiency also enhances the metabolism of solvents. An increasing number of dietary supplements, fruit juices, and vegetable components are being identified as inducers or inhibitors of cytochrome P-450s (Huang and Lesko 2004). Flavonoids in grapefruit juice were one of the first documented classes of naturally occurring cytochrome P-450 inhibitors. Other potent inhibitors are bergamottin, echinacea, and some constituents of *Ginkgo biloba* (Chang et al. 2006).

Fasting for 1-3 days can significantly enhance the hepatotoxicity of medium to high doses of VOCs that undergo metabolic activation. Fasting results in decreased hepatic concentrations of glutathione because of cessation of intake of amino acids required for its synthesis. Glutathione plays a key role in detoxifying electrophilic metabolites of a number of VOCs, such as 1,1-DCE (Jaeger et al. 1974). Conversely, conjugation of glutathione with TCE or PCE can lead to limited formation of cytotoxic, mutagenic metabolites (see section "Metabolic Activation and Inactivation"). Withholding food for 12-24 h also results in induction of CYP2E1, the major catalyst of activation of many VOCs. Bruckner et al. (2002) found that lack of food intake during sleep results in lipolysis and formation of acetone, an effective CYP2E1 inducer, in rats. The animals were thus more susceptible to acute carbon tetrachloride hepatotoxicity during their initial waking hours. Long-term food deprivation (starvation), however, results in reduced synthesis of CYP2E1 and other cytochrome P-450s and decreased metabolic activation of VOCs.

Physical activity can significantly influence the toxicokinetics of solvents. Exercise increases two of the key determinants of uptake of inhaled VOCs: (1) respiratory and alveolar ventilation rate and (2) cardiac output and pulmonary blood flow. Exercise can double pulmonary uptake of VOCs (Astrand 1983), although this is often not considered in setting occupational exposure standards. Blood flow to the liver and kidneys is diminished with exercise, so biotransformation of well-metabolized solvents decreases. A PBTK model for methylene chloride predicted that light exercise would result in a doubling of blood concentrations of methylene chloride and of metabolite formation via cytochrome P-450- and glutathione-dependent pathways (Dankovic and Bailer 1994).

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Ethanol is an effective CYP2E1 inducer when ingested repeatedly in substantial amounts (Lieber 1997). There are numerous reports of marked potentiation of hepatic or renal damage by ethanol or other alcohols in persons occupationally exposed to potent hepatorenal toxicants, such as carbon tetrachloride (Folland et al. 1976; Manno et al. 1996). A group of moderate drinkers exposed to 1,1,1-trichloroethane vapor at 175 ppm showed a significant increase in metabolism and metabolic clearance of the chemical (Johns et al. 2006). 1,1,1-Trichloroethane is a relatively nontoxic solvent. Kaneko et al. (1994) exposed ethanol-pretreated rats by inhalation to TCE or 1,1,1-trichloroethane at 50-1,000 ppm. 1,1,1-Trichloroethane metabolism was enhanced at all vapor concentrations, but TCE metabolism was enhanced by ethanol only at the highest concentration (1,000 ppm). The researchers concluded that alterations in the rate of biotransformation of low doses of well-metabolized VOCs, such as TCE, are of little consequence toxicologically because their biotransformation is perfusion-limited (limited by hepatic blood flow); most of the TCE entering the liver is metabolized, even in nondrinkers who still have CYP2E1 in excess for the small amounts of TCE arriving in the blood. Kedderis (1997) used a PBTK model to predict that a 10-fold increase in CYP2E1 activity in humans inhaling TCE at 10 ppm would result in only a 2% increase in TCE metabolism by the liver. Thus, increased bioactivation capacity due to ethanol or other factors should not increase risks of toxicity or cancer in Camp Lejeune residents because of their low exposures to TCE, 1,1-DCE, methylene chloride, vinyl chloride, benzene, or other extensively metabolized VOCs. As previously described in this chapter, PCE is poorly metabolized, although some of its metabolites are cytotoxic or mutagenic. Kedderis (1997) predicted that a 10-fold increase in CYP2E1 activity in humans inhaling PCE, as opposed to TCE, at 10 ppm would result in a 3.8-fold increase in formation of PCE metabolites in the liver. Enzyme induction would result in increased health risks posed by PCE.

It should be recognized that the timing of ethanol consumption and VOC exposure is important. Prior repeated exposure to ethanol is necessary for substantial CYP2E1 synthesis to occur. Concurrent exposure to ethanol and a VOC, however, may sometimes be protective against both well-metabolized and poorly metabolized solvents. VOCs and ethanol are both metabolized by CYP2E1, so the two xenobiotics compete for the available isozyme. That situation is known as competitive metabolic inhibition. Muller et al. (1975) observed that concurrent intake of ethanol and inhalation of TCE at 50 ppm by human subjects resulted in a marked decrease in urinary excretion of TCE's major metabolites, trichloroacetic acid and trichloroethanol. In this instance, ethanol would afford protection against TCE's oxidative metabolites. Metabolism of ethanol produces an excess of nicotinamide adenine dinucleotide, a cofactor that favors formation of trichloroethanol from chloral hydrate, at the expense of trichloroacetic acid. Reduced formation of trichloroacetic acid would be protective against trichloroacetic acid-induced hepatic tumors. Larson and Bull (1989), however, observed that interaction in rats only with very high doses of TCE and ethanol.

Medications and drugs of abuse that induce or inhibit CYP2E1 and other enzymes involved in the metabolism of VOCs can potentially alter the chemicals' toxicity or carcinogenicity. Phenobarbital and other barbiturates were among the first recognized cytochrome P-450 inducers. Notable inducers of CYP2E1 include, in addition to alcohols and acetone (Gonzalez 2007), acetaminophen, salicylates, phenytoin, chlorpromazine, isoniazid, and diazepam. Nakajima et al. (1992) showed that pretreatment of rats with phenobarbital, ethanol, or 3-methylcholanthrene significantly increased TCE oxidation. The same would be expected to occur in humans at high TCE doses. Again, cytochrome P-450 induction will probably not be of consequence at the concentrations found in the water supplies at Camp Lejeune. Some drugs (such as cycloheximide, disulfiram, and chloramphenicol) and the aforementioned natural constituents of plants inhibit CYP2E1. Those compounds, in sufficient doses, would be protective against high doses of TCE and other VOCs that are bioactivated by CYP2E1.

Tobacco smoke contains a number of compounds that are strong cytochrome P-450 inducers. Polycyclic hydrocarbons, such as 3-methylcholanthrene, are potent inducing agents. The polycyclic hydrocarbons primarily stimulate synthesis of CYP1A1 and CYP1A2, cytochrome P-450 isozymes that play a modest role in catalyzing the biotransformation of TCE (Nakajima et al. 1992). Nicotine, however, is a

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strong CYP2E1 inducer in rats (Micu et al. 2003). Cigarette smoke is known to induce CYP2E1 in both rodents and humans.

Diseases

Illness can be a major source of variability in a person's response to VOCs. Impaired metabolism and systemic clearance of xenobiotics are commonly seen in persons with hepatitis or cirrhosis. Reduction in metabolic capacity results from decrease in liver mass, reduced enzymatic activity, or diminution in liver blood flow. Lower concentrations of CYP2E1, CYP1A2, and glutathione are found in cirrhotic livers (Murray 1992). Lower cytochrome P-450-mediated bioactivation of VOCs can be protective, but reduced capacity to conjugate their electrophilic metabolites would have the opposite effect.

Chronic renal disease has become more prevalent in the United States over the last decade (Coresh et al. 2007). Progressive loss of renal function will lead to impaired renal excretion of some potentially toxic or carcinogenic metabolites, such as trichloroacetic acid. Trichloroacetic acid is highly bound to albumin and other plasma proteins. Plasma-protein binding is reduced in patients with compromised renal function, apparently because of renal retention of substances that compete with trichloroacetic acid for protein-binding sites and because of reduced albumin synthesis. Thus, decreased formation of trichloroacetic acid from TCE and PCE and reduced plasma-protein binding would increase systemic clearance. That may be offset, however, by a decrease in renal excretion (Yuan and Venitz 2000). Impairment of renal bioactivation of glutathione metabolic intermediates of TCE and PCE by oxidation or β-lyase (see section "Metabolic Activation and Inactivation") would be protective (Bruckner et al. 2008).

Diabetes mellitus is a metabolic disease characterized by hyperglycemia as a result of insulin deficiency (type I) or insulin resistance (type II). Type II diabetes accounts for 90% of cases in the United States. Animal experiments show that type II diabetes increases susceptibility to the toxicity of certain solvents apparently because of inhibition of tissue repair (Sawant et al. 2004). The human relevance of these animal findings is uncertain. CYP2E1 induction is a prominent effect of type I diabetes in rats but not in humans. Type II diabetes results in CYP2E1 induction in humans (Lucas et al. 1998; Wang et al. 2003).

Obesity has been shown to result in induction of CYP2E1 in both rats and humans. Rats made obese by the feeding of an energy-rich diet were found to have higher hepatic catalytic activities for a number of CYP2E1 substrates (Raucy et al. 1991). The systemic clearance of chlorzoxazone, a CYP2E1 substrate, was recently shown to be more rapid in rats on a high-fat diet than in normal rats and more rapid in obese rats than in those on the high-fat diet (Khemawoot et al. 2007). CYP2E1 activity in hepatic and adipose-tissue microsomes of the animals followed the same order. Ketone bodies were increased in obese rats, as they were in diabetic animals that had fasted. Two ketone bodies, acetone and β-hydroxybutyrate, are CYP2E1 inducers. O'Shea et al. (1994) observed that ketone bodies were also increased in the blood of volunteers who had fasted. They found that obesity in people was associated with increased 6-hydroxylation of chlorzoxazone. Lucas et al. (1998) similarly observed higher CYP2E1-mediated hydroxylation of chlorzoxazone in 17 obese patients; such people may be at increased risk for cytotoxicity and tumorigenicity from moderate to high, but not very low, VOC exposure.

In summary, a number of factors may influence the toxicokinetics and, in turn, the adverse effects of TCE, PCE, and other VOCs. Much research has focused on factors that alter the metabolic activation or inactivation of those chemicals. Consumption of a high-fat diet and obesity can induce (increase the activity of) CYP2E1. Fasting, smoking, ethanol ingestion, acetone exposure, and several drugs induce CYP2E1 activity in the liver and other tissues. CYP2E1 induction can increase the toxic or carcinogenic potency of very high doses of some VOCs (such as TCE and PCE). That does not occur after low exposures to TCE and other well-metabolized VOCs (such as benzene, vinyl chloride, and methylene chloride). CYP2E1 induction, however, may increase the potency of slowly metabolized VOCs, such as PCE. Some drugs and the constituents of some foods inhibit CYP2E1 and would be protective against oxidative metabolites of most VOCs.

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INTERACTIONS

Many occupational and environmental exposures to VOCs involve multiple chemicals. That is particularly true of contaminated environmental media, in that widespread use of solvents leads to their volatilization and their entry into surface waters and groundwater. A major portion of VOCs spilled onto the ground evaporates. Some, however, leaches through soil into groundwater and remains trapped there. The groundwater at about 90% of 1,608 hazardous-waste sites on the U.S. National Priorities List contains VOCs. TCE is the most frequently found of all chemicals, followed by lead, PCE, and benzene (Fay and Mumtaz 1998). The most common four-component VOC mixture is TCE, PCE, 1,1,1-trichloroethene, and 1,1-dichloroethane. ATSDR (2004) published a toxicologic profile addressing potential health risks posed by that four-component mixture. Many U.S. cities' drinking-water supplies also contain complex mixtures of VOCs. Total concentrations range from parts per trillion to parts per billion (Moran et al. 2007). Trace amounts (less than 1 ppb) of a variety of VOCs are present in the blood of many nonoccupationally exposed members of the general population (Churchill et al. 2001; Blount et al. 2006).

Exposure to multiple VOCs and possibly other chemicals raises the question of the consequences of chemical interactions for human health. Most studies have involved experiments with binary or ternary mixtures. One chemical may have no effect on, potentiate (enhance), or antagonize (inhibit) adverse actions of a second or third chemical. Knowledge of mechanisms of VOC interactions involves largely the influence of one VOC on the metabolic activation or inactivation of another. Koizumi et al. (1982) published the results of one of the first such studies. They found that coexposure of rats to PCE and 1,1,1,-trichloroethane resulted in significant suppression of 1,1,1,-trichloroethane metabolism. Workers exposed to TCE and PCE were found to have lower urinary concentrations of TCE metabolites than workers exposed to TCE alone (Seiji et al. 1989). Such an interaction resulted from competitive metabolic inhibition, wherein the amounts of the combined chemicals exceeded the metabolic capacity of the study subjects. Such an interaction is protective against cytotoxicity and carcinogenicity in that the bioactivation of both TCE and PCE is reduced. Conversely, systemic concentrations of the parent compounds would be increased, and this might increase neurologic effects.

PBTK modeling has been used by several research groups to predict the metabolic and toxicologic consequences of exposure to VOC mixtures. Competitive metabolic inhibition was evident in a PBTK-model approach to studying TCE and 1,1-DCE (El-Masri et al. 1996) and TCE and vinyl chloride (Barton et al. 1995). Later PBTK modeling efforts predicted interaction thresholds below which competitive metabolic inhibition would not occur. Dobrev et al. (2001), for example, reported that the thresholds for interaction of TCE with PCE and 1,1,1,-trichloroethane vapor in rats were 25 and 135 ppm, respectively, when the TCE concentration was 50 ppm. Those findings imply that protection from adverse effects would occur in occupational settings when vapor concentrations were relatively high. An increase in blood TCE concentrations under these exposure conditions was predicted to result in a disproportionate increase in formation of nephrotoxic glutathione conjugation products in humans (Dobrev et al. 2002). Other PBTK modeling approaches are being developed to simulate the metabolic outcome of human exposures to up to four common VOC water pollutants (for example, TCE, PCE, chloroform, and 1,1,1-trichloroethane) (Mayeno et al. 2005). Competitive metabolic inhibition, with potentiation or protection from adverse effects of VOCs, would not occur at much lower exposure concentrations. Competitive metabolic inhibition and antagonism of (protection from) adverse effects of the VOCs would not occur at much lower exposures, such as those at Camp Lejeune.

Additivity of toxic effects of chemicals that act by similar mechanisms is typically assumed in the absence of experimental evidence to the contrary. There does not appear to be experimental evidence of greater than additive interactions of VOCs (ATSDR 2004). One possible mechanism of potentiation is induction of CYP2E1 by one or more members of a VOC mixture. Experiments in rats dosed with single VOCs have shown that most of the compounds are not effective inducers of CYP2E1 or other cytochrome P-450 isozymes. Competitive metabolic inhibition, as described above, would result in antagonism of (that is, less than additive) adverse effects if metabolites are the bioactive moieties. Goldsworthy and

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Popp (1987) found that the joint effect of TCE and PCE on peroxisome proliferation in the liver and kidneys of mice and rats was less than additive. Stacey (1989) studied the joint action of TCE and PCE on the liver and kidneys of rats. Combined administration of near-toxic-threshold doses of the two solvents produced modest hepatorenal toxicity. Jonker et al. (1996) provided evidence that TCE and PCE in combination with two other similarly acting solvents affected kidney weight in rats given subtoxic doses of each chemical by gavage for 32 days. Competitive metabolic inhibition at relatively high exposure levels of toluene, ethylbenzene, and xylene has been predicted by PBTK modeling to result in higher internal exposures (and CNS depressant effects) than would occur with simple additivity (Dennison et al. 2005). Although experimental data are limited, the assumption of additivity of potential risks posed by VOC water contaminants at Camp Lejeune seems to be a reasonable, prudent approach.

A few toxicity or carcinogenicity studies of complex chemical mixtures, including VOCs, have been conducted. The National Toxicology Program (NTP 1993) supplied F-344 rats and B6C3F$_1$ mice with drinking water containing 25 contaminants for up to 26 weeks. The mixture contained TCE, PCE, methylene chloride, 1,1,1-trichloroethane, 1,1-DCE, 1,1-dichloroacetic acid, other solvents, heavy metals, polychlorinated biphenyls, and a phthalate. The total no-observed-adverse-effect levels for histologic changes in organs were 11 ppm in rats and 378 ppm in mice. Suppression of immune function occurred in female mice that consumed the mixture at 756 ppm for 2 weeks or 378 ppm for 13 weeks. Constan et al. (1996) saw centrilobular hyperplasia and apoptosis in the livers of rats after 1 mo. A followup study in chemically tumor-initiated rats showed that the contaminant mixture did not promote preneoplastic foci in the liver (Benjamin et al. 1999). Wang et al. (2002) supplied ICR mice with water containing chloroform, 1,1-dichloroacetic acid, 1,1-DCE, 1,1,1-trichloroethane, TCE, and PCE for 16 and 18 mo. There was a trend of increasing frequency of hepatocellular neoplasms in the male mice and increasing incidence of mammary adenocarcinomas in the high-dose female mice. The total concentration of VOCs in the drinking water of females was about 1,555 ppb. Most of the mixture was TCE (471 ppb) and PCE (606 ppb). Those concentrations are far lower than have previously been reported to produce tumors. The results must be regarded as preliminary in that the study design had a number of limitations, and the results have not been replicated. In addition, male B6C3F$_1$ mice are particularly susceptible to hepatic tumors, and mice metabolically activate a substantially greater proportion of solvent doses than do humans.

Multiple VOCs and other chemicals are commonly present in trace amounts (parts per trillion to parts per billion) in water from contaminated wells in the United States. The Environmental Protection Agency, in the absence of information to the contrary, assumes that any adverse effects of chemicals that act by the same mechanism are additive. Several VOCs act on some organs by similar mechanisms. Animal experiments with high doses of combined VOCs have shown that one VOC inhibits the metabolic activation (that is, protects against adverse effects) of the other. That would not occur at the lower concentrations that were found in the water supplies at Camp Lejeune.

SUMMARY

Residents of homes supplied with contaminated water can be exposed orally by drinking the water, as well as by inhalation and dermal exposure when using heated water for bathing, showering, and washing clothes and dishes. Experiments with TCE and chloroform have shown that ingestion and inhalation make comparable contributions to systemically absorbed doses, and the contribution from skin absorption is minor.

The concept of dose has been refined to three components: administered, or external dose; systemically absorbed, or internal dose; and target organ and tissue dose. It is most important to specify the dose of the bioactive moiety, whether it is the parent compound or one or more metabolites. Concurrent pharmacokinetic processes, including absorption, tissue distribution, binding, metabolism, and elimination, determine tissue doses. One or more of these processes can vary significantly from one route of exposure to another, from one species to another, and from one person to another. Understanding how these processes differ can factor into predicting toxicity and cancer risks for various exposure scenarios.

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PCE, TCE, and other VOCs are quickly and extensively absorbed from the gastrointestinal tract. These small, uncharged, lipophilic molecules rapidly diffuse through membranes from areas of higher to lower concentration. It is typically assumed that 100% of doses of orally administered VOCs are absorbed. A portion of VOCs reaching the pulmonary blood are exhaled before reaching the arterial circulation. Pulmonary and hepatic first-pass elimination acting in concert are responsible for removing almost 90% of very low doses of TCE, thereby affording extrahepatic organs protection from noncancer and cancer effects from trace concentrations of such chemicals in drinking water. Less protection from poorly-metabolized VOCs (for example, PCE) is afforded. The pattern of consumption of contaminated water can substantially influence the toxicologic outcome. Differences in the type of controlled exposure used in animal studies compared with intermittent exposures in humans raises the question of the relevance of such cancer bioassay results to real-life human exposures.

TCE, PCE, and other VOC vapors are also very well absorbed from the lungs. Pulmonary absorption is largely determined by the chemical's blood:air partition coefficient, the animal's alveolar ventilation rate, and its cardiac output. The rats' TCE blood:air partition coefficient is almost three times that of humans. Resting alveolar ventilation rates and cardiac outputs are markedly higher in mice than in rats and significantly higher in rats than in humans.

Metabolism plays a key role in modulating the kinetics, and in turn the injury potential of VOCs. These chemicals can be biotransformed to more toxic or less toxic derivatives. The majority of metabolism occurs in the liver. TCE and PCE are metabolized by two primary metabolic pathways: cytochrome P-450s-catalyzed oxidation and glutathione *S*-transferase-mediated conjugation. The oxidation pathway accounts for the majority of metabolism of low-to-moderate doses of TCE and PCE. Oxidative metabolites are largely responsible for liver and lung toxicity and carcinogenicity. GSH conjugation becomes more prominent when high doses begin to saturate oxidation. TCE and PCE are metabolized quite similarly, although PCE is somewhat more potent because of formation of additional toxic products. Oxidative activation of TCE and PCE is much greater in mice and rats than in humans. Metabolic activation by the GSH pathway is substantially greater in rats than in humans. It is well-established that rodents absorb more inhaled TCE and PCE, metabolically activate a greater proportion, and detoxify epoxide metabolites less efficiently than humans.

It is not clear whether infants and children are more susceptible to adverse effects of VOCs. Age-dependent changes in pharmacokinetics and pharmacodynamics may make an immature human more or less sensitive, depending upon the individual's age, the chemical, and the organ system. Low concentrations of CYP2E1 in neonates and infants will result in increased TCE concentrations but low concentrations of oxidative metabolites. Conversely, children have a relatively large liver and high liver blood flow, placing them at greater risk than adults from effects of oxidative metabolites. Age-related changes in one toxicokinetic process may be augmented or offset by concurrent changes in other processes. Cells in developing organs (for example, neurons in the brain) are more sensitive to injury. Thus, toxicant exposure during such a "window of susceptibility" can have serious, long-lasting consequences. The net effect of anatomical and physiologic immaturities is difficult to predict, particularly for classes of chemicals (for example, VOCs) for which there is very little information from animal or human studies.

The net effect of toxicokinetic and toxicodynamic changes during aging is the major determinant of susceptibility of geriatric populations. It has been predicted with a PBTK model that PCE exposure will result in increased PCE concentrations in the elderly. Unfortunately, there are even fewer experimental data from geriatric humans or animals with which to verify outcomes than there are data from pediatric populations. Additional compounding factors in the elderly include use of multiple medications, poor nutrition, and preexisting disease states.

Women do not appear to differ substantially from men in their responses to TCE, PCE, and other VOCs. Metabolism of solvents is not sex-dependent, but higher female body-fat content results in accumulation of higher body burdens of the lipophilic chemicals and increased formation of their metabolites. Relatively little is known about the influence of pregnancy on maternal and fetal disposition of VOCs and their metabolites. Animal models, however, show lower maternal TCE metabolism during pregnancy and limited fetal exposure to oxidative metabolites.

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A variety of genetic polymorphisms in human populations can affect the quantity and quality of CYP450 and glutathione *S*-transferase enzymes and, in turn, the outcomes of exposure to solvents. There are marked interindividual differences in activity of hepatic CYP2E1, the primary isozyme responsible for metabolic oxidation of TCE. This interindividual difference is not believed to be toxicologically significant, however, for persons exposed to very low concentrations of TCE and other well-metabolized VOCs. The interindividual difference in oxidative capacity may be important, however, in the extent of metabolic activation and response to poorly-metabolized VOCs, such as PCE.

Lifestyle can potentially influence an individual's responses to VOCs in a number of ways. Dietary habits and components, physical activity, ethanol intake, and certain drugs can affect metabolism and deposition of solvents. Serious illness, impaired metabolism and systemic clearance of parent compounds, and obesity are some additional factors that can affect the way the body handles exposure to TCE and PCE.

Many occupational and environmental exposures to VOCs involve multiple chemicals. Knowledge of mechanisms of chemical interactions largely involves the effect of one VOC on the metabolic activation of a second. Concurrent exposures to sufficiently high doses typically involve competitive metabolic inhibition, which results in increased concentrations of parent compounds and lower production of metabolites. Such interactions will not occur at very low exposure concentrations.

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4

Review of Toxicologic Studies

This chapter summarizes findings of animal studies of trichloroethylene (TCE) and tetrachloroethyle (perchloroethylene, PCE) toxicity and relevant end points. The review was based in part on previously published comprehensive reviews on the two chemicals of interest, but numerous published studies were reviewed individually in greater detail. Studies were examined according to criteria that reflected robustness of study design related to the hypothesis being tested and that included such characteristics as number of animals tested, measurement methods used, appropriateness of statistical methods, and concordance of conclusions with data presented. Studies substantially lacking in some of or all those and other measures of study quality and studies whose outcomes were not able to be repeated in later studies or in other laboratories were given less weight in the evaluation. Salient findings on principal health end points are summarized by chemical and organ system. The administered doses or the doses associated with the no-observed-adverse-effect levels (NOAELs) or the lowest-observed-adverse-effect levels (LOAELs) are reported when possible. At the conclusion of this toxicologic review, a hazard evaluation of TCE and PCE exposure at Camp Lejeune was conducted for selected health end points. A hazard evaluation is conducted to provide information on the intrinsic toxic potential of an exposure and is not meant to provide a quantitative risk assessment.

As noted in Chapter 2, the committee identified nine volatile organic compounds (VOCs) of concern. To manage the vast amount of information on each, we provide different degrees of review according to the findings from the exposure assessment regarding the frequency and concentrations of the contaminants in the affected drinking-water systems. This chapter presents detailed toxicologic evaluations of the two chemicals of greatest concern, TCE and PCE. Information on the metabolism of TCE and PCE and factors that influence their toxicity was presented in Chapter 3 and is drawn upon in this chapter. Chapter 7 provides an integrated discussion of the toxicologic evidence in context with the epidemiologic evidence on TCE and PCE. For completeness of the literature review, Appendix D provides brief reviews of the toxicologic data on the seven other chemicals.

TRICHLOROETHYLENE

Data on the toxicity of TCE were summarized in a report by the National Research Council (NRC 2006). In some cases, more recent literature reviews on particular subjects were available (e.g., Lamb and Hentz 2006; Watson et al. 2006), and they were relied on for defining the body of literature available up to the time of publication. In addition, a literature search of Medline was done to determine whether any relevant new publications were available. Conclusions drawn for the present report were based on a review of the body of available peer-reviewed literature. Because TCE and PCE have some of the same metabolites and effects, salient finding of studies of PCE are discussed in relevant sections of the TCE review. More detailed review of the PCE literature is provided later in the chapter. To facilitate a comparison of the toxicologic data with the epidemiologic data in Chapter 7, the toxicologic data are pre-

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sented below according to organ system and in some sections divided to consider toxic effects separately from carcinogenic effects.

Hepatic Effects

Toxicity

TCE, even in high doses, produces only a modest degree of injury of hepatocytes in laboratory animals. Klaassen and Plaa (1966) compared the acute hepatotoxicity of TCE with that of other common halogenated aliphatic hydrocarbons (halocarbons) in male mice dosed by intraperitoneal injection. The dose of TCE required to produce an increase in serum alanine-aminotransferase activity, 1.6 mL/kg, was almost as high as the dose that was lethal in 50% of test animals, 2.2 mL/kg. Oxidative stress was assessed by measuring thiobarbituric-acid-reactive substances in the livers of male Fischer rats that received one intraperitoneal injection of TCE at 0, 100, 500, or 1,000 mg/kg (Toraason et al. 1999). Thiobarbituric-acid-reactive substances were increased in the 500- and 1,000-mg/kg groups. Hepatic concentrations of 8-hydroxy-2′-deoxyguanosine adducts, induced in DNA by oxygen-based radicals, were also increased at 500 mg/kg and presumably at 1,000 mg/kg. It should be recognized that the 500- and 1,000-mg/kg doses produced stage II and stage III-IV anesthesia, respectively. Channel et al. (1998) gave male B6C3F$_1$ mice TCE at 0, 400, 800, or 1,200 mg/kg in corn oil by gavage 5 days/week for 8 weeks. Transient increases in cell and peroxisome proliferation, centered around day 10, were observed only at the highest dose. There were no differences from controls in the incidences of hepatocellular apoptosis or necrosis. Thiobarbituric-acid-reactive substances were significantly increased in the groups treated with TCE at 800 and 1,200 mg/kg on days 6-14. 8-Hydroxy-2′-deoxyguanosine adducts in liver DNA were significantly increased throughout much of the study with TCE at 1,200 mg/kg. Buben and O'Flaherty (1985) saw a modest increase in serum alanine aminotransferase and decrease in hepatic glucose-6-phosphatase activity in mice given TCE at 500 mg/kg or greater in corn oil by gavage five times a week for 6 weeks. Mice receiving as little as 100 mg/kg per day had an increase in relative liver weight. It is clear that TCE, even when given repeatedly to mice and rats at narcotic doses, has little ability to damage hepatocytes.

Adverse effects of TCE on the liver are usually attributed to metabolites of the cytochrome P-450-mediated oxidative pathway (Bull 2000). Buben and O'Flaherty (1985) reported that plots of their mouse subchronic-hepatotoxicity data against urinary-metabolite excretion values indicated that TCE's effects are directly related to the extent of its metabolism. As described in Chapter 3, TCE is oxidized by cytochrome P-450s (notably CYP2E1 at low to moderate TCE doses) to chloral, which is converted to chloral hydrate. That intermediate has a short half-life; it is rapidly oxidized to trichloroacetic acid, which is reduced to trichloroethanol (Lash et al. 2000a). Relatively small amounts of dichloroacetic acid may arise from trichloroacetic acid or other metabolites. Induction of CYP2E1 in rats with pyridine increases the toxicity of TCE to isolated rat hepatocytes (Lash et al. 2007). High concentrations of trichloroacetic acid and dichloroacetic acid are not toxic to hepatocytes freshly isolated from B6C3F$_1$ mice (Bruschi and Bull 1993); the researchers proposed that trichloroacetic acid and dichloroacetic acid cause peroxisome proliferation and the ensuing generation of reactive moieties that deplete glutathione and can cause oxidative injury. Dichloroacetic acid does not induce peroxisome proliferation in male B6C3F$_1$ mice in the same dose range at which it produces hepatic tumors (DeAngelo et al. 1999). Laughter et al. (2004) found that high oral doses of TCE increased liver weight, peroxisome proliferation, and hepatocellular proliferation in male mice. Those effects appeared to be due primarily to trichloroacetic acid's activating a nuclear protein known as the peroxisome-proliferator-activated receptor alpha (PPARα). PPARα-dependent changes seen in gene expression may contribute to the carcinogenicity of TCE in mouse liver.

TCE-induced hepatic injury is not a common finding in humans and was rarely reported in patients when TCE was used as an anesthetic (Lock and Reed 2006). Clearfield (1970) described hepatocellular degeneration in two men who intentionally inhaled extremely high vapor concentrations of TCE for their intoxicating effects. In contrast, James (1963) saw only small foci of fatty accumulation in the liver

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(steatosis) of a man who died after 10 years of TCE abuse. Bruning et al. (1997) found renal injury but no evidence of hepatotoxicity in a man rendered unconscious for 5 days by drinking about 70 mL of TCE in a suicide attempt. Pembleton (1974) reported a transient postoperative rise in serum aspartate aminotransferase activity in four of 100 patients anesthetized with TCE for surgical procedures. A study of 289 British workers who experienced central nervous system (CNS) symptoms from TCE inhalation and dermal exposure in the workplace revealed no clear diagnoses of hepatotoxicity (McCarthy and Jones 1983). Such findings over the last 50 years indicate that acute or repeated high-dose exposures to TCE will produce a modest degree of hepatic injury in some people but not in most people (ATSDR 1997a).

Cancer

The carcinogenic effects of TCE and its metabolites have been assessed in a number of lifetime studies of several strains of mice and rats (NCI 1976; Fukuda et al. 1983; Henschler et al. 1984; Maltoni et al. 1986; NTP 1988, 1990a). Results of studies of TCE induction of hepatic tumors in rodents are summarized here on the basis of the extensive National Research Council review (NRC 2006).

It has been well established that TCE, when administered chronically in very high doses by gavage, can produce an increased incidence of hepatocellular cancer in $B6C3F_1$ mice. In the original bioassay (NCI 1976), technical grade TCE (containing epichlorohydrin and 1,2-epoxybutane as stabilizers) had this effect. Concern that these stabilizers are well-established mutagens and contributed to TCE's apparent carcinogenicity led scientists to utilize TCE without these stabilizers in future bioassays. Henschler et al. (1984) saw no increase in liver tumors in either sex of Swiss ICR/HA mice, rats, or Syrian hamsters that inhaled highly-purified TCE (stabilized with 0.0015% triethanolamine) for 18 months. Exposure of male and female $B6C3F_1$ mice to epichlorohydrin-free TCE by corn oil gavage at 1,000 mg/kg/day for 2 years caused increases in hepatocellular carcinoma. No such increase in liver tumor incidence was manifest in F344/N rats (NTP 1990a). Another study of four additional strains of rats of both sexes ingesting epichlorohydrin-free TCE at 125-1,000 mg/kg also showed no increase in liver tumors (NTP 1988). Thus, it has been demonstrated that TCE itself, when administered chronically in very high oral doses, results in an increased incidence of liver cancer limited to male and female $B6C3F_1$ mice.

The major oxidative metabolites of TCE—trichloroacetic acid, dichloroacetic acid, and chloral hydrate—have also been extensively studied in rodents (Herren-Freund et al. 1987; Bull et al. 1990; DeAngelo et al. 1991, 1996, 1997, 1999; Daniel et al. 1992, 1993; Pereira 1996; George et al. 2000; NTP 2002a,b,c; Leakey et al 2003). Trichloroacetic acid is a species-specific carcinogen that induces peroxisome proliferation and hepatocellular carcinomas when administered in drinking water to male and female $B6C3F_1$ mice ($B6C3F_1$ mice are particularly susceptible) (Herren-Fruend et al. 1987; Bull et al. 1990; DeAngelo et al. 1991). The blood concentration of trichloroacetic acid required to induce hepatic tumors in mice is in the millimolar range. Effects have been observed with drinking-water concentrations of trichloroacetic acid of 0.05-5 g/L. TCA did not induce hepatic tumors in male F344 rats under similar treatment conditions (Daniel et al. 1993; DeAngelo et al. 1997). $B6C3F_1$ mice produce a large amount of trichloroacetic acid after exposure to TCE relative to unresponsive mouse strains (see Chapter 3). Trichloroacetic acid increases the rate of hepatocellular proliferation, production of reactive oxygen species, hepatocellular hyperplasia, and hepatomegaly (see Chapter 3). Marked species differences in susceptibility to peroxisome proliferation associated with liver cancer after increased fatty-acid beta oxidation and modulation of hepatocellular replication related to activation of the PPARα nuclear receptor by TCE and its metabolites have been investigated and reviewed in detail (Klaunig et al. 2003; Cattley 2004; Laughter et al. 2004). Rats exhibit saturation of TCE oxidative metabolism that results in amounts of trichloroacetic acid that are probably insufficient to induce hepatic peroxisome proliferation. It is thought that humans, like rats, have lower rates of oxidative metabolism and higher rates of conjugation than do mice.

Trichloroacetic acid produces hepatic tumors only in $B6C3F_1$ mice, but dichloroacetic acid induces them in mice and in F344 rats at exposures up to 5 g/L in drinking water for 104 weeks (Herren-Freund et al. 1987; Bull et al. 1990; Daniel et al. 1992; DeAngelo et al. 1996, 1999; Pereira 1996; NRC

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2006). Dichloroacetic acid is a major metabolite of TCE in $B6C3F_1$ mice but a minor metabolite in Sprague-Dawley rats (Larson and Bull 1992). Marked liver enlargement and cytomegaly in dichloroacetic acid-treated mice also indicate that induction of hepatic tumors depends on stimulation of increased cell division secondary to hepatoxoic damage (Bull et al. 1990). Inhibition of dichloroacetic acid metabolism by the parent compound at less than 1 to 500 μM (Kato-Weinstein et al. 1998) is thought to contribute to the variation in mouse hepatic tumors observed at this dose range (Bull et al. 2002).

Choral hydrate induces hepatic tumors in male $B6C3F_1$ mice but not in female mice or F344 male rats (George et al. 2000; NTP 2002a,b; Leakey et al. 2003). Female $B6C3F_1$ mice given choral hydrate in water by oral gavage for 104 weeks at up to 100 mg/kg per day had no increase in hepatic tumors (NTP 2002a), whereas exposure at the same doses in two groups of male mice fed ad libitum (NTP 2002a,b) or fed a calorie-controlled diet (Leakey et al. 2003) had increased incidences of hepatocellular adenoma or carcinoma (combined). Dietary control of caloric intake in the latter study was thought to improve survival and to decrease interassay variation. Choral hydrate is metabolically converted to trichloroacetic acid or dichloroacetic acid, and this contributes to its weak carcinogenicity. Overall, choral hydrate is an ineffective hepatic carcinogen that induces tumors only in male mice.

An epidemiologic study was conducted of short-term clinical exposure to choral hydrate used as a hypnosedative and possible cancer risk in humans (Haselkorn et al. 2006). An increasing risk of prostatic cancer with chloral hydrate was found, but the trend wat not statistically significant. Thus, the authors concluded that there was no persuasive evidence of a causal relationship between choral hydrate exposure and cancer in humans, but they were unable to rule out a causal relationship because statistical power was low. Trichloroacetic acid elicits hepatic tumors in mice with a phenotype typical of peroxisome proliferators, whereas dichloroacetic acid produces hepatic tumors with a distinctly different phenotype and also increases tumor growth (Bull 2000; Thai et al. 2003).

The relevance of TCE- and PCE-induced hepatic tumors to humans has been the subject of a great deal of research. Oral and inhalation carcinogenicity bioassays of TCE in rodents have shown that adenocarcinomas are strain- and species-specific (that is, are limited to the $B6C3F_1$ mouse). Haseman et al. (1998) reported a spontaneous hepatic-tumor incidence of 42.2% in male control $B6C3F_1$ mice used in National Toxicology Program (NTP) studies. The NTP recently held a series of workshops to determine whether another mouse strain and a rat strain should be adopted. In light of the high background hepatic-tumor incidence, it was recommended that the NTP explore the use of multiple mouse strains (King-Herbert and Thayer 2006).

It has been clearly established that the toxicokinetics (target-organ dosimetry) of TCE and PCE of the mouse and the human are different (see Chapter 3). Mice absorbed substantially more TCE and PCE because of their greater respiratory and alveolar ventilation rate, cardiac output and pulmonary blood flow rate, and blood:air partition coefficient. Mice also metabolically activate substantially more of their absorbed doses to bioactive substances (Lipscomb et al. 1998). On an equivalent inhalation exposure to PCE, rats exhibited markedly higher blood and urinary concentrations of trichloroacetic acid and dichloroacetic acid than humans (Volkel et al. 1998). The rats' blood also contained much higher concentrations of protein adducts (Pahler et al. 1999). Physiologically based toxicokinetic models similarly predict that mice will produce higher target-organ (liver) doses of trichloroacetic acid than humans after exposure to PCE (Clewell et al. 2005) and TCE (Clewell and Andersen 2004).

The primary mode of action of trichloroacetic acid, and to a smaller extent dichloroacetic acid, is activation of PPARα. Stimulation of PPARα can enhance DNA replication, resulting in expansion of some clones of hepatocytes and suppression of apoptosis, so initiated and precancerous cells will be spared. Male wild-type mice dosed orally with TCE exhibit hepatocyte proliferation and changes in expression of genes involved in cell growth (Laughter et al. 2004). PPARα-null mice are refractory to those effects, which are associated with carcinogenesis. Mice expressing human PPARα fail to show increases in markers of cell proliferation and are resistant to liver cancer if treated with PPARα agonists (Morimura et al. 2006; Yang et al. 2008). The concentration of PPARα in human cells is about 10% of that in the livers of rodents (Palmer et al. 1998; Klaunig et al. 2003; Lai 2004). The interpretation of mouse hepatic-tumor induction in 2-year bioassays relative to the inducing compound's mode of action, including induc-

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tion of peroxisome proliferation, has been assessed in a human-relevance framework (Cohen et al. 2003, 2004; Meek et al. 2003; Holsapple et al. 2006; Meek 2008). The relevance of $B6C3F_1$ mouse hepatic tumors to humans is also weakened by the observations that the background incidence of hepatic tumors in unexposed $B6C3F_1$ mice is about 60% and that large numbers of chlorinated compounds induce such tumors in mice (Gold and Slone 1995). The human is likely to be much less responsive toxicodynamically than the mouse to the cellular effects of trichloroacetic acid and dichloroacetic acid.

Many toxicologists have judged that the mode of action for hepatic carcinogenesis observed in mice after administration of peroxisome-proliferation-inducing drugs and other chemicals (such as TCE and PCE) makes it unlikely that such chemicals pose a hepatic-cancer risk in humans (Cattley et al. 1998; NTP 2000; Clewell and Andersen 2004; NRC 2006; Klaunig et al. 2007). It was concluded by the National Research Council that the PPARα mode of action for liver cancer in mice is not relevant to humans (NRC 2006). However, others have raised questions about the interpretation of PPARα actions and whether it is the only relevant mode of action for such chemicals (Keshava and Caldwell 2006), and this continues to be a subject of active debate (Peters et al. 2005; Klaunig et al. 2007; NRC 2008).

Toxicodynamic mechanisms of hepatic carcinogenicity other than peroxisome proliferation have been explored. Both trichloroacetic acid and dichloroacetic acid apparently contribute to hepatic tumorigenesis in mice (Bull et al. 2002; Caldwell and Keshava 2006). High, repeated doses of those TCE and PCE metabolites initially stimulate and then depress the growth of normal liver cells (Bull 2000). That may confer a growth advantage on initiated cells. Dichloroacetic acid at high concentrations also appears to act by increasing the clonal expansion and decreasing apoptosis of such precancerous cells. Moderate amounts of dichloroacetic acid are apparently produced from trichloroacetic acid and trichloroethanol in mice, but only trace amounts were found in one of three studies of TCE-exposed humans (see Chapter 3). It is important to recognize that stimulation or inhibition of cell growth through PPARα activation ceases when the metabolites are eliminated (Miller et al. 2000). Thus, such alteration of cell signaling is not a genotoxic mechanism of action. Very high concentrations of dichloroacetic acid and chloral hydrate have a weak genotoxic action in vitro. Bull (2000) and Moore and Harrington Brock (2000), however, conclude that it is unlikely that those metabolites would cause tumors in any organ through genotoxocity or mutagenicity at exposure concentrations relevant to humans.

Renal Effects

Toxicity

TCE has limited capacity to produce renal injury in rodents that are subjected to high oral exposures for extended periods. Jonker et al. (1996), for example, gave female Wistar rats TCE at 500 mg/kg by corn-oil gavage for 32 consecutive days. Urinalyses showed only slight increases in *N*-acetyl-β-glucosaminidase and alkaline phosphatase activities. A comparable exposure to PCE produced somewhat larger increases. Kidney weights were modestly increased by both chemicals. Microscopic examination revealed multifocal areas of vacuolation and karyomegaly in the animals' renal tubules. Male Eker rats received TCE at 50, 100, 250, 500, or 1,000 mg/kg by corn-oil gavage 5 times a week for 13 weeks (Mally et al. 2006). There were no changes in γ-glutamyltransferase activity or other urinary indexes of renal cytotoxicity. There was tubular-cell proliferation at 250 mg/kg or greater and karyomegaly at 500 mg/kg or greater. Overt nephropathy was restricted to the 1,000-mg/kg group. Nephropathy has been a common finding in rats and mice in chronic, high-dose cancer bioassays of TCE (NCI 1976; NTP 1986a, 1988, 1990a). Nephrosis and cytomegaly were more severe in the rats than in the mice, and male rats were generally affected more severely than females. Cytomegaly was manifested as frank enlargement of the cytoplasm and the nucleus of scattered tubular cells in the inner cortex and outer stripe of the medulla. Karyomegaly was later observed in the proximal tubular epithelial cells of the pars recta. The affected tubules were dilated, and the cells were flattened and elongated and contained enlarged, hyperchromatic

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nuclei with irregular shapes. A low incidence of renal tumors was seen consistently in several strains of male rats in the bioassays.

TCE has also been found to have some adverse renal effects when inhaled acutely or repeatedly at high concentrations for long periods. Proximal tubular damage was reported in male F344 rats exposed for 6 h to TCE vapor at 1,000 or 2,000 ppm (Chakrabarti and Tuchweber 1988). Mensing et al. (2002) subjected male F344 rats to TCE at 500 ppm for 6 h/day 5 days/week for 6 months. Glomerulonephritis was seen on histopathologic examination, but urinary biomarkers of glomerular damage were not found. Increases in urinary *N*-acetyl-β-glucosaminidase and low-molecular-weight proteins reflected mild proximal tubular damage.

Adverse effects of TCE on the kidneys are due largely to metabolites formed via the glutathione conjugation pathway (Lash et al. 2000b). As described in Chapter 3, conjugation of TCE with glutathione to form *S*-(1,2-dichlorovinyl)glutathione (DCVG) occurs primarily in the liver. DCVG is secreted into bile and blood. That in the bile is converted to *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), which is reabsorbed into the bloodstream. As noted in Chapter 3, humans have a lower capacity than rats to metabolize TCE by the glutathione pathway. Lash et al. (1999) were able to detect DCVG in the blood of humans who had inhaled TCE at 50 or 100 ppm for 4 h, but Bloemen et al. (2001) could not find DCVG or DCVC in the urine of similarly exposed subjects. DCVG in the blood is taken up by the kidneys and metabolized to DCVC by γ-glutamyltransferase and a dipeptidase. Lash et al. (2001b) observed the following decreasing order of toxic potency in freshly isolated rat cortical cells: DCVC > DCVG >> TCE. DCVC can be detoxified by acetylation and activated further by two pathways: (1) cleavage by renal cytosolic and mitochondrial β-lyases to dichlorothioketene, which in turn can lose a chloride ion to yield chlorothioketene or tautomerize to form chlorothionacyl chloride (the latter two moieties are very reactive and acylate proteins and DNA), and (2) oxidation by renal cytochrome P-450s or flavin-containing monoxygenases to the epoxide, DCVC sulfoxide (DCVCS). Lash et al. (1994) reported that DCVCS was a more potent nephrotoxin than DCVC in vitro and in vivo in rats. Apoptosis was observed after as little as 1 h of incubation of cultured human renal proximal tubular cells with DCVC and DCVCS (Lash et al. 2003, 2005). Cellular proliferation accompanied by increased expression of proteins associated with cellular growth, differentiation, stress, and apoptosis was also an early response to low doses. Necrosis, however, was a late, high-dose phenomenon in this cell system. Exposure of human renal proximal tubular cells to DCVC at lower concentrations for 10 days also resulted in expression of genes associated with cell proliferation, apoptosis, and stress (Lash et al. 2005) and repair and DCVC metabolism (Lash et al. 2006).

Proximal tubular-cell damage, as discussed above, appears to be a prerequisite for renal-cell cancer. Bruning et al. (1996) observed urinary protein-excretion patterns indicative of tubular damage in all of a group of 17 workers exposed for years to peak TCE vapor concentrations that caused CNS depression. They later reported small increases in urinary excretion of glutathione *S*-transferase α and α_1-microglobulin in a group of 39 cardboard workers without renal-cell cancer who had been heavily exposed to TCE for about 16 years (Bruning et al. 1999). Both indexes are markers of proximal tubular injury. Higher α_1-microglobulin excretion was reported in renal-cell cancer patients with TCE exposure than in renal-cell cancer patients without TCE exposure in an updated study (Bolt et al. 2004). Green et al. (2004) described similar findings in 70 electronics workers who inhaled TCE at an average concentration of 32 ppm for about 4 years. A battery of tests for nephrotoxicity was assessed after 4 days of exposure. Urinary albumin and *N*-acetyl-β-glucosaminidase were higher than in controls, although there was no correlation with the magnitude or duration of TCE exposure. There was also a suggested increase in urinary glutathione *S*-transferase α activity that correlated with the intensity but not with the years of exposure. Finally, Bruning et al. (1998) evaluated renal damage in a man who ingested about 70 mL of TCE in a suicide attempt. He was rendered unconscious for 5 days. His urinary glucose and protein concentrations were normal, but α_1- and β_2-microglobulin, *N*-acetyl-β-glucosaminidase, and several low-molecular-weight protein concentrations were increased. Such modest, reversible signs of renal injury demonstrate that TCE, even in extreme exposure conditions, has quite small nephrotoxic potential in humans.

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Cancer

TCE was given in corn oil to F344/N rats and B6C3F$_1$ mice of both sexes by oral gavage at doses up to 1,000 mg/kg in rats and 6,000 mg/kg in mice in a 13-week study and up to 1,000 mg/kg in both species and sexes in a 103-week study (NTP 1990a). Two-year oral-gavage studies in four additional rat strains were also conducted (NTP 1988). Nonneoplastic renal lesions were found in all animals dosed for 2 years. In all strains of rats tested, cytomegaly and karyomegaly of tubular cells in the renal corticomedullary region were observed. Frank toxic nephropathy was observed with higher frequency beginning at 52 weeks of exposure. A statistically significant increase in renal-tumor incidence was observed only in male F344/N rats exposed to TCE at 1,000 mg/kg for 2 years (this was the LOAEL). TCE has been shown to cause toxicity in proximal renal tubules in vivo; results of in vitro studies have also indicated toxicity of TCE and its metabolite DCVC in primary cultures of rat tubular cells (Cummings et al. 2000).

Nephrotoxicity was reported in Long-Evans rats after 6 months of inhalation exposure to TCE at 500 ppm (Mensing et al. 2002). The urinary-protein profile reported is consistent with impairment of tubular reabsorption of filtered protein. Inhalation studies were conducted in both sexes of Sprague-Dawley rats with TCE at 100, 300, and 600 ppm for 2 years and in Swiss mice at 100 and 600 ppm for 78 weeks (Maltoni et al. 1988a). Renal adenocarcinomas were reported in male rats at 600 ppm (the LOAEL), but no renal effects were observed in mice. Cytokaryomegaly or megalonucleocytosis was observed at the end of 2 years of exposure in male rats (77% of the 600-ppm group and 17% of the 300-ppm group) with no indication of pathologic conditions earlier.

Inconclusive evidence of induction of $\alpha_{2\mu}$-globulin by TCE, formic acid formation, or peroxisome proliferation as a mechanism or mode of action of TCE as a renal carcinogen was found (Goldsworthy et al. 1988; Green et al. 2003).

Results of animal studies indicate that kidney cancer occurs at high doses (for example, 1,000 mg/kg and 600 ppm) in male rats and is preceded by nephrotoxicity affecting the proximal tubule. An analysis by the U.S. Environmental Protection Agency with pooling across strains indicated a modest tumor effect in female rats (EPA 2001). Renal-cell cancers observed in German workers who were highly exposed to TCE have generally been assumed to be due to an initiating genotoxic effect of DCVC or DCVC coupled with the promoting effects of recurring cytotoxicity and compensatory hyperplasia (Bruning and Bolt 2000). The complete TCE glutathione conjugation pathway and assumed penultimate nephrotoxic metabolites are described in Chapter 3. It has been proposed that exposures below nephrotoxic concentrations or some threshold of exposure probably pose no risk of cancer in that nephrotoxicity is deemed to be a prerequisite for development of kidney cancer (Bruning and Bolt 2000; Harth et al. 2005). TCE oxidative metabolizing enzymes (such as CYP2E1 and CYP3A5 isoforms) have polymorphic forms. Known human population diversity in bioactivation and detoxification capabilities is an additional consideration in determining the exposure concentration below which nephrotoxicity is unlikely. For TCE inhalation exposure in the occupational setting, the suggested practical threshold below which nephrotoxicity is unlikely to occur is 250 ppm as an 8-h time-weighted average (Harth et al. 2005).

In humans, inactivation of the von Hippel-Landau (*VHL)* tumor-suppressor gene is responsible for the hereditary *VHL* cancer syndrome. Affected people are predisposed to a variety of tumors; more than 80% of sporadic renal-cell carcinomas are associated with inactivation of this gene. Brauch et al. (2004) noted that renal-cell cancer patients unexposed to TCE did not have the somatic *VHL* gene mutational characteristics of TCE-exposed renal-cell cancer patients. According to Moore and Harrington-Brock (2000), TCE itself has little if any mutagenic potential, and it is unlikely that any TCE-induced tumors would be mediated by its major oxidative metabolites. TCE recently also yielded negative results when tested in a *Salmonella typhimurium* strain (Ames test) that contained DNA coding for cytochrome P-450 reductase, cytochrome b5, and cytochrome P-450 2E1 (Emmert et al. 2006). TCE glutathione-conjugated metabolites DCVG and DCVC have, however, been shown to have genotoxic effects in in vitro test systems.

A recent study provides insight into a TCE renal-carcinogenesis threshold proposal. A strain of rats (Eker) uniquely susceptible to renal carcinogens was exposed to TCE at an administered dose of 100,

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250, 500, and 1,000 mg/kg by gavage 5 days/week for 13 weeks (Mally et al. 2006). The Eker rat is a unique animal model for renal-cell carcinoma, carrying a germ-line alteration of the *Tsc-2* tumor-suppressor gene. Results showed a significant increase in cell proliferation in renal tubular cells but no increased preneoplastic renal lesions or tumor incidence. In vitro studies were conducted on primary Eker rat renal epithelial cells by exposing them to the TCE metabolite DCVC dissolved in water at 10-50 µM for 8, 24, and 72 h. Concentrations of DCVC that reduced rat renal-cell survival to 50% also resulted in cell transformation. No carcinogen-specific mutations were identified in the *VHL* or *Tsc-2* tumor-suppressor genes in the transformed cells. Renal-cell carcinomas in the Eker rat have substantial similarities to human renal-cell carcinomas. It is not entirely clear that this or any contemporary experimental animal model adequately mirrors humans with regard to the effects of TCE-induced mutations in the *VHL* gene, but the authors firmly suggest that TCE-mediated renal carcinogenicity may occur only secondarily to nephrotoxicity and sustained regenerative cell proliferation. The latter findings, coupled with the aforementioned data of Lash et al. (2005, 2006), suggest that renal-cell cancer may result from prolonged, high-dose cytotoxicity and sustained cell proliferation but that TCE's metabolites may lack initiating activity.

Both DCVC and its mercapturic acid metabolite *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine have been found in urine of humans exposed to TCE, and illustrates that the glutathione conjugation pathway is active (Bernauer et al. 1996). Exposure of volunteers to TCE at 50 or 100 ppm showed that DCVG concentrations were 3.4 times higher in males than in females (Lash et al. 1999). Genes associated with stress, apoptosis, cell proliferation, repair, and DCVC metabolism were up-regulated almost double in cultured human renal tubular cells exposed to subcytotoxic doses of DCVC for 10 days (Lock et al. 2006). Male rats display higher reduced glutathione conjugation, γ-glutamyl transpeptidase, and cysteine conjugate β-lyase activity than female rats. Taken together, results in the cited studies indicate that male humans and male rats both possess significant glutathione conjugation capacity and can produce the critical TCE metabolite DCVC; renal carcinoma has been observed in male rats and male workers when both have been exposed to high TCE concentrations for prolonged periods of time. These observations show data congruence, indicating that the conjugation pathway plays a central role in induction of renal carcinoma in males of both species. As discussed in Chapter 3, rats have greater capacity to metabolically activate TCE by this pathway than humans.

Evaluation of potential risks to human health related to contaminants in water supplies is a central concern of this project. Given the foregoing, it is sensible to begin to apply recent toxicologic information to contemporary maximum environmental values. In summary, exposure to high TCE concentrations appears to lead to saturation of the oxidative metabolic pathway with an attendant pronounced increase in metabolism via the glutathione-dependent pathway and likely increased production of penultimate toxic metabolites, such as DCVC sulfoxide, chlorothioketene, and thionoacylchloride from DCVC (Dobrev et al. 2002). As previously described, substantially larger quantities of these toxic moieties are produced from TCE by rat kidney than by human kidney. In addition, cultured rat cortical cells have been shown to be more susceptible to DCVC-induced necrosis than cultured human proximal tubular cells (Lash et al. 2001a). Human kidney cells have the capacity to metabolically activate and to respond adversely to low concentrations of DCVC, but not to the extent exhibited by male rat kidneys.

Pulmonary Effects

Toxicity

The pulmonary-toxicity potential of TCE has been studied extensively in mice and rats; there appear to be no reports of TCE-induced lung injury in humans. Forkert et al. (1985) were among the first scientists to describe lung toxicity in mice. Intraperitoneal injection of very high doses of TCE (2,000 and 2,500 mg/kg) into male CD mice rapidly caused damage of bronchiolar Clara cells and alveolar type II cells, anesthesia, and a marked reduction in pulmonary cytochrome P-450 content. Female CD-1 mice

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inhaling TCE at 20-2,000 ppm 6 h/day for up to 5 days exhibited dose-dependent vacuolation of Clara cells (Odum et al. 1992). Pyknosis of the bronchiolar epithelium also occurred at the higher concentrations. No morphologic changes were seen in the lungs of rats that were exposed to TCE vapor at 500 or 1,000 ppm. Isolated mouse Clara cells metabolized TCE to chloral, trichloroacetate, and trichloroethanol, but no trichloroethanol glucuronide was detected. It was proposed that the inability of these cells to conjugate trichloroethanol with glucuronic acid led to accumulation of chloral to cytotoxic concentrations (Odum et al. 1992; Green 2000). Forkert et al. (2005) found that oxidation of TCE to chloral was catalyzed in murine lung microsomes by cytchrome P-450s 2E1, 2F2, and 2B1. Forkert et al. (2006) later demonstrated that bioactivation of TCE by CYP2E1 and CYP2F2 occurred in Clara cells. Dichloroacetyl lysine adducts were localized in Clara cells in the TCE-treated CD-1 mice, and CYP2E1 and CYP2F2 are highly concentrated there (Forkert 1995). It is generally accepted that the cytotoxicity and possibly the weak mutagenicity of chloral and diacetyl chloride contribute to the development of lung tumors in mice.

The mouse appears to be uniquely sensitive to TCE-induced pulmonary toxicity and cancer. Mice, but not rats, developed lung tumors in the inhalation bioassays conducted by Fukuda et al. (1983) and Maltoni et al. (1988a). Clara cells are numerous and present throughout the airways of mice. They are found much less frequently in rats and are rare in humans (Green 2000). Mouse Clara cells contain considerable amounts of smooth endoplasmic reticulum, a membrane network in which cytochrome P-450s are bound. Human Clara cells are largely devoid of this organelle. Accordingly, metabolic activation of TCE to chloral is high in mouse, much lower in rat, and undetectable in human microsomes (Green et al. 1997b). Green et al. measured high CYP2E1 concentrations in mouse lung microsomes; concentrations of CYP2E1 were lower in rats and undetectable in humans. Mace et al. (1998), however, were able to detect very low concentrations of CYP2E1 mRNA and protein in human peripheral lung tissue. Forkert et al. (2005) found that male CD-1 mouse lung microsomes efficiently metabolize TCE to chloral hydrate, whereas the reaction was observed—at low rates—in samples from only three of eight human donors. Those findings suggest that TCE poses only a minimal risk of pulmonary toxicity in humans.

Cancer

TCE inhalation exposure caused an increased incidence of pulmonary tumors in ICR, Swiss, and B6C3F$_1$ mice but not in rats or hamsters. When female ICR mice were exposed to TCE at 150 and 450 ppm 7 h/day 5 days/week for 104 weeks followed by an observation period of 3 weeks, lung-tumor incidence increased by a factor of 3 (Fukuda et al. 1983); epichlorohydrin was used as a TCE stabilizer in this experiment. Female Sprague-Dawley rats exposed at the same concentrations for the same period had no increase in lung tumors. Male Sprague-Dawley rats had no increase in lung tumors but did have an increase in testicular and renal tumors after exposure to TCE at 600 ppm for 104 weeks but not at 100 or 300 ppm (Maltoni et al. 1986). Excess lung tumors were observed in Swiss mice and B6C3F$_1$ mice exposed to TCE at up to 600 ppm for 78 weeks (Maltoni et al. 1988a). Five gavage studies were also reviewed for induction of lung tumors in several strains of rats and mice; no excess lung tumors were found (NRC 2006). These results, the information presented in the preceding section on pulmonary toxicity, and the lack of reports of pulmonary injury and cancer in workers suggest that the risk of lung cancer in TCE-exposed human populations is minimal.

Genotoxicity

TCE is a weak genotoxicant in a number of test systems (Bruning and Bolt 2000; Moore and Harrington-Brock 2000; NRC 2006). Genotoxicity generally includes mutational end points, cytogeneticity, and primary DNA damage, whereas mutagenicity refers to the ability to induce heritable mutations. TCE oxidative metabolites trichloroacetic acid, dichloroacetic acid, and chloral hydrate generally have shown weak or no reactivity in mutagenicity tests; the weight of evidence in both in vitro and in vivo test sys-

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tems indicates that mutations are probably not key events in induction of cancer by these compounds (Moore and Harrington-Brock 2000). TCE was negative in a *Salmonella typhimurium* test strain that had cytochrome P-450 2E1 metabolizing capacity (Emmert et al. 2006).

Neonatal B6C3F$_1$ mice were given chloral hydrate, trichloroacetic acid, and TCE by intraperitoneal injection at the ages of 8 and 15 days; their livers were examined for 8-hydroxy-2′-deoxyguanosine 24 and 48 h and 7 days after the final dose (Von Tungeln et al. 2002). Mice treated with trichloroacetic acid or chloral hydrate showed significantly higher DNA-8-hydroxy-2′-deoxyguanosine adduct formation related to lipid peroxidation or oxidative stress; the authors concluded that male neonatal B6C3F$_1$ mice are not sensitive to induction of liver cancer by these compounds.

Significant increases in DNA migration in the Comet assay and micronuclei formation were reported in human HepG2 cells after treatment with TCE at 0.5-4 mM (Hu et al. 2008). Increases in both 8-hydroxy-2′-deoxyguanosine-DNA adducts and thiobarbituric acid-reactive substances were observed; depletion of glutathione increased susceptibility to TCE-induced effects, whereas cotreatment with *N*-acetylcysteine prevented the effects. That indicated that oxidative stress probably played a role in TCE-induced genotoxic damage in those cells. Hypomethylated DNA was found in both dichloroacetic acid-promoted and trichloroacetic acid-promoted mouse hepatic tumors in an initiation-promotion experiment (Tao et al. 2004). Gene expression controlling cell growth, tissue remodeling, and xenobiotic metabolism was altered in in dichloroacetic acid-induced mouse hepatic tumors (Thai et al. 2003). Overall evidence indicates that TCE and the oxidative metabolites trichloroacetic acid, dichloroacetic acid, and chloral hydrate are unlikely to act primarily by a mutational or genotoxic mechanism as hepatic carcinogens.

The TCE glutathione conjugate DCVC has been shown to have genotoxic effects, including increased reverse mutations in *S. typhimurium* tester strains, unscheduled DNA synthesis, and formation of DNA adducts in vitro (Bruning and Bolt 2000; Moore and Harrington-Brock 2000). Genotoxicity measures in rodent kidneys and primary cultures of human renal cells showed significant dose-dependent increases in results of the Comet assay (DNA single-strand breaks and alkali-labile sites) and in micronuclei frequency with subtoxic concentrations of TCE (Robbiano et al. 2004). Among the six rodent renal carcinogens tested, TCE was among the ones that exhibited the lowest potency for these end points; nonetheless, the results indicated that TCE is genotoxic in renal cells isolated from rats and humans. In another experiment, rats were exposed to TCE by inhalation or to DCVC by oral gavage. Proximal tubules isolated from kidneys of treated rats were assessed for DNA damage with the Comet assay (Clay 2008). Positive controls were included to demonstrate the sensitivity of the assay. Test results with TCE indicated a negative response in this assay. DCVC showed slight effects in a few animals 2 h after treatment and at the highest dose tested (10 mg/kg), but the effects were not strong enough to be considered positive. On the basis of those findings and other published data, the authors concluded that renal tumors seen in bioassays are nongenotoxic in origin.

Reproductive Effects

Toxicity

Studies in Males

Several studies of the reproductive effects of TCE have been conducted, and many of these were reviewed by the National Research Council (NRC 2006). Zenick et al. (1984) found reduced copulatory behavior in male rats after an oral dose of 1,000 mg/kg per day 5 days/week for 6 weeks but indicated that the changes may have been related to the narcotic effects of TCE. Mice exposed to TCE by inhalation 4 h/day for 5 days (Land et al. 1981) showed an increased percentage of abnormal sperm at 2,000 ppm, the highest dose tested (about 3,000 mg/kg per day) and no increase at 200 ppm (about 300 mg/kg per day). Kumar et al. (2000a,b) exposed male Wistar rats by inhalation to 376 ppm for 12 or 24 weeks (4 h/day 5 days/week) and reported decreased epididymal sperm count and motility, reduced testosterone concentra-

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tions, and lower fertility when the treated rats were mated with untreated females. There were also significant reductions in body weight, testicular weight, total cauda epididymal sperm count, and percentage of motile sperm; the effects were greater after 24 weeks than after 12 weeks of exposure. By 24 weeks, the testes were atrophied and had smaller seminiferous tubules. Sertoli cells were present, but tubules contained no spermatocytes, and spermatids and Leydig cells were hypoplastic (Kumar et al. 2001). Xu et al. (2004) exposed male mice by inhalation to TCE at 1,000 ppm 6 h/day 5 days/week for 1-6 weeks and found no effects except for a significant reduction in the fertilizing ability of sperm from the TCE-exposed males when they were combined in vitro with eggs from superovulated control females or when the males were mated with superovulated control females. A study in male rabbits (Veeramachaneni et al. 2001) reported that a mixture of several agents, including TCE, caused alterations in mating desire and ability, sperm quality, and Leydig-cell function. The effects were assessed subjectively, and it is difficult to determine the contribution of TCE to the changes seen.

Forkert et al. (2002) demonstrated that CYP2E1 is involved in the metabolism of TCE to chloral in Leydig cells and epididymides. Greater sensitivity of the mouse epididymis to high TCE vapor exposures correlated with greater chloral formation and higher concentrations of CYP2E1 in the epididymis than in the testis. Forkert et al. (2003) later found CYP2E1 in human epididymal epithelium and Leydig cells. Seminal-fluid samples from eight TCE-exposed mechanics who had diagnoses of clinical infertility contained TCE and some of its oxidative metabolites. More recently, Kan et al. (2007) evaluated epididymal damage by TCE at the light-microscopic and electron-microscopic levels in mice after inhalation at 1,000 ppm for 1 day or for 1, 2, 3, or 4 weeks. The study showed epithelial sloughing and degeneration with separation of the seminal tubules from the basement membrane after exposure for 1 week or more. Epididymal damage became more severe with increasing duration of exposure. DuTeaux et al. (2003) found CYP2E1 and dichloroacetyl adducts in the epididymis and afferent ducts, which were indicative of the formation of reactive cytotoxic metabolites in the cells that were damaged. The absence of mitochondrial β-lyase and the lack of formation of protein adducts in the epididymis and afferent ducts of rats dosed with DCVC suggest that TCE metabolites formed via the glutathione conjugation pathway do not participate in male reproductive toxicity. DuTeaux et al. (2004a,b) investigated the bioactivation of TCE and adduct formation in the testis and epididymis. In male rats ingesting TCE at estimated doses of 1.6-2.0 and 3.4-3.7 mg/kg per day in drinking water for 14 days, there was a dose-dependent reduction in capacity for in vitro fertilization of ova from untreated females. That effect occurred in the absence of any apparent alteration in the sperm other than a dose-dependent increase in oxidized proteins. The increase in lipid peroxidation implicates CYP2E1-mediated formation of reactive metabolites as a mechanism of toxicity.

Studies in Females

Manson et al. (1984) exposed female rats orally by gavage to TCE at 10, 100, or 1,000 mg/kg per day for 2 weeks before mating, 1 week during mating, and throughout gestation. Although high concentrations of TCE were measured in fat, adrenal glands, and ovaries, and uterine tissue contained high concentrations of trichloroacetic acid, female fertility was not affected. However, 17% of females in the high-dose group died, and weight gain was significantly reduced. Neonatal survival was also significantly reduced at the high dose, particularly in female offspring.

Cosby and Dukelow (1992) conducted a study of oral exposure of pregnant mice to TCE at 24 or 240 mg/kg per day during gestation and in vitro fertilization studies with TCE, trichloroacetic acid, dichloroacetic acid, and trichloroethanol. No effects were noted in the in vivo study; in the in vitro studies, there was a dose-related decrease in the percentage of fertilized embryos with trichloroacetic acid, dichloroacetic acid, and trichloroethanol but not with TCE.

Female rats were exposed to several male reproductive toxicants, including TCE, at 0.45% in drinking water for 2 weeks (Berger and Horner 2003). Oocytes collected after induced ovulation were incubated with sperm from unexposed males. The percentage of oocytes fertilized, the number of pene-

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trating sperm per oocyte, and the ability of oocytes to bind sperm plasma membrane proteins were all significantly reduced.

Studies in Mating Pairs

The NTP (1986b,c) conducted fertility-assessment-by-continuous-breeding studies of TCE dietary exposure in mice and rats. The feed for both studies contained microencapsulated TCE at 0.15%, 0.30%, and 0.60%. In mice, the body weights of male F_1 pups and the combined body weights of male and female F_1 pups were significantly reduced in the 0.60% group. Sperm motility was reduced in the F_0 parental males at the highest dose, but no other reproductive effects were seen. There were changes in testis and epididymis weight, increased liver weight, and increased combined kidney and adrenal weight. F_0 females showed no reproductive effects but had increased liver weight. Treatment-related lesions were seen in the livers and kidneys of both males and females. Increased perinatal mortality was seen in the F_1 pups at the highest dose level (NTP 1986b). In rats, there was a statistically significant trend toward reduced numbers of litters per pair, and crossover mating was reduced if either of the parents was treated. General signs of toxicity included reduced body-weight gain, altered testis and epididymis weight, and increased relative liver weight and kidney and adrenal weight at all doses (NTP 1986c).

Cancer

The majority of chronic carcinogenicity bioassays of TCE in rodents have failed to reveal an increased incidence of testicular tumors. Maltoni et al. (1988a) did, however, report a dose-related increase in Leydig-cell tumors in male Sprague-Dawley rats exposed to TCE vapor at 100, 300, or 600 ppm for 104 weeks. The biologic significance of findings in that investigation has been discounted because of methodologic and statistical deficiencies (ATSDR 1997b). The NTP (1986a, 1988) reported the findings of a 2-year bioassay in which four strains of rats were gavaged with TCE at 0, 500, or 1,000 mg/kg 5 days/week. Only Marshall rats exhibited a dose-related increase in Leydig-cell tumors. Leydig-cell adenoma is the most frequently encountered testicular tumor in mice and rats (Cook et al. 1999). The incidence varies from 1-5 % in control Sprague-Dawley rats to nearly 100% in F344 rats. Almost all those neoplasms are benign and occur in older rats. Most human testicular tumors are of germ-cell or Sertoli-cell origin and occur in young or middle-aged men. Leydig-cell tumors are rare in men (Cook et al. 1999). Thus, spontaneous or TCE-induced Leydig-cell tumors in rats are of questionable relevance to humans.

In summary, the 2006 National Research Council report concluded that TCE is toxic to spermatogenesis and the fertilizing ability of sperm. A detailed review by Lamb and Hentz (2006) concluded that male reproductive effects were generally seen at high concentrations that cause systemic toxicity and are more frequent in mice than in rats. The LOAEL for male reproductive effects after inhalation exposure is 376 ppm for 12 weeks (4 h/day 5 days/week) in rats, and there is general toxicity at that exposure. A NOAEL of 200 ppm for 5 days (4 h/day) was reported in mice in the Land et al. (1981) study, but no data for determining general toxicity were available. The LOAEL in rats for oral exposure is 1.6 mg/kg per day for 14 days in drinking water, but the relevance to humans of effects on in vitro fertilizing capacity is unclear. At 1,000 mg/kg, there were effects on copulatory behavior but with concomitant narcosis. No oral NOAEL was identified.

The oral NOAEL for female fertility in mice was 240 mg/kg per day in in vitro fertilization studies and in rats was 1,000 mg/kg per day with exposure before and during mating and during gestation. The LOAEL for impaired fertility in studies in which both males and females were exposed was about 145 mg/kg per day in rats and 875 mg/kg per day in mice. There was an indication of systemic toxicity at those doses. The NOAEL was about 70 mg/kg per day in rats and 405 mg/kg per day in mice.

Additional studies of the reproductive toxicity of TCE are needed to permit better identification of LOAELs and NOAELs in both male and female rats and mice. In addition, more work on the mechanisms of action and potency of the various metabolites is needed.

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Developmental Effects

Pregnancy Outcomes

Several studies of TCE and metabolic products in rodents and avian species were reviewed in the 2006 National Research Council report. Early rodent studies using inhalation exposure (Schwetz et al. 1975; Dorfmueller et al. 1979) indicated little or no developmental toxicity as a result of exposure, whereas later studies by Dawson et al. (1990, 1993) and Johnson et al. (1998a,b, 2003) reported an increase in cardiovascular malformations at concentrations as low as 0.25 ppm. However, the latter studies used direct delivery of TCE to the gravid uterus or in drinking water and a novel examination process for examining the heart and great vessels. Fisher et al. (2001), using the same examination process as the Dawson and Johnson groups and in collaboration with them, reported no increase in cardiac or vascular defects. Warren et al. (2006) examined fetuses from the Fisher et al. (2001) study and found no ocular defects after TCE exposure. More recently, Carney et al. (2006), using a standard test protocol (inhalation exposure to TCE at 0, 50, 150, or 600 ppm for 6 h/day on gestation days 6-20), reported no effect of TCE on development in rats at up to 600 ppm, a concentration that produced minimal maternal toxicity.

Collier et al. (2003) showed changes in gene expression during cardiac development after TCE exposure, and Klaunig et al. (1989) reported that TCE inhibited in vitro gap-junction-mediated intercellular communication. Coberly et al. (1992) used the chimera assay and showed no effects of TCE in mouse preimplantation embryos. There is evidence from one laboratory that direct administration of the metabolites trichloroacetic acid and dichloroacetic acid to pregnant rats increased congenital cardiac defects in their offspring (Smith et al. 1989, 1992; Epstein et al. 1992); effects were observed at doses of 330 mg/kg per day and greater over multiple days and at single doses of 1,900-3,500 mg/kg.

Several in vitro rodent and avian studies have shown effects of TCE on embryonic development, and these models have been used to investigate potential mechanisms for TCE and metabolite effects. For example, Saillenfait et al. (1995) reported concentration-dependent decreases in growth and differentiation indexes and increases in morphologic abnormalities in rat whole-embryo cultures, and Boyer et al. (2000), Hoffman et al. (2004), and Drake et al. (2006a,b) reported on TCE effects in a chick model. Changes in eye, pharyngeal arches, and cardiovascular development could be seen at high exposure concentrations (such as 80-250 ppm). In most cases, the TCE metabolites trichloroacetic acid and dichloroacetic acid were also studied and found to be at least as effective as TCE. Drake et al. (2006a,b) studied the effects of timing of TCE yolk-sac injection on chick heart development and found a greater effect if exposure occurred during endocardial cushion formation (Hamburger Hamilton [HH] stages 13-20) than if exposure occurred at earlier stages of development (HH stages 3+-17). Those authors also reported hypercellularity and increased proliferation in the outflow tract and atrioventricular canal of the heart. However, Mishima et al. (2006), using chick whole-embryo organ culture and TCE at low concentrations (10-80 ppm) in medium, reported reduction in mesenchymal cells in endocardial cushions. Ou et al. (2003), using an in vitro bovine organ culture, showed that TCE reduced heat-shock protein interactions with endothelial nitric oxide synthase, causing the synthase to shift to superoxide-anion generation, and inhibited vascular endothelial-cell proliferation stimulated by endothelial growth factor. Those effects on endothelial function are important in the development of cardiac defects. Although the in vitro studies are important in understanding the mechanism of TCE effects on development, their relevance for hazard characterization is unknown.

The recent studies by Carney et al. (2006) address some of the recommendations of the 2006 National Research Council report that additional studies are needed to evaluate a LOAEL. The Carney study clearly shows no effects on heart or other organ development in the rat at exposure concentrations up to a minimal maternally toxic concentration. Several studies have been published to address mode of action but have not made clear which species is most appropriate for human modeling. Otherwise, the more recent data reviewed here do not change the conclusions of the 2006 National Research Council report on the prenatal toxicity of TCE. An in-depth review of the animal and human data on cardiovascular defects by Watson et al. (2006) concluded that there is no indication of a causal link between TCE and cardiovas-

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cular defects at environmentally relevant concentrations. On the basis of that review and the Carney et al. (2006) study results, the conclusion is appropriate.

In summary, the database on the prenatal developmental effects of TCE is robust and indicates a lack of pregnancy outcomes up to concentrations that are minimally toxic in adults. The in vitro and whole-embryo studies are intriguing, but effects reported in them are probably due to the degree of exposure. On the basis of the Carney et al. (2006) study, the LOAEL of inhalation exposure during prenatal development in rats is greater than 600 ppm, and the NOAEL is also 600 ppm. The LOAEL for maternal or adult toxicity is 600 ppm, and the NOAEL is 150 ppm.

Growth and Development

A few studies have examined the neurologic effects of TCE after developmental exposure. For example, rat pups from dams exposed during gestation and lactation to TCE in drinking water at 312 mg/L (about 30 mg/kg per day) showed a reduction in 2-deoxyglucose uptake in the brain, indicating a reduction in glucose uptake or brain metabolism (Noland-Gerbec et al. 1986). Taylor et al (1985) showed an increase in activity of 60- and 90-day-old rats whose dams were exposed to TCE at 312 mg/L and above during gestation and lactation. In a followup study, Isaacson and Taylor (1989) reported that TCE at similar doses in rats reduced the amount of myelin in the dorsal hippocampus and proposed that the change might account for the behavioral effects of TCE. Another study by Isaacson et al. (1990) involved dosing young rats beginning at weaning with TCE in drinking water (312 mg/L) for 4 weeks, then with distilled water for 4 weeks. A second group was treated with TCE in drinking water for 4 weeks, distilled water for 2 weeks, then TCE for 2 weeks (as adults). Animals in the second group, but not the first group, showed reduced latency and improved learning in a Morris water maze. Both groups showed reduced hippocampal myelin. All those studies used small numbers of animals, and the dose was unclear, but they suggest neurologic effects of developmental exposure to TCE (see further discussion in the next section).

A study by Peden-Adams et al. (2006) reported immunotoxicity after developmental exposure of mice to TCE at 0, 1,400, or 14,000 ppb in drinking water from gestational day 0 through the age of 3 weeks or 8 weeks. There was a decreased plaque-forming-cell response in males at both ages and doses and a decreased plaque-forming-cell response in females exposed to TCE at 1,400 ppb at the age of 8 weeks and at 14,000 ppb at both ages. Reduced numbers of splenic B220 cells were seen in 3-week-old pups exposed at 14,000 ppb. There was an increase in all thymic T-cell types ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$, and $CD4^-/CD8^-$) at 8 weeks and increased delayed-type hypersensitivity in females at both concentrations and in males at only the high dose. This was the first study to report developmental immunologic effects at lower concentrations than in adults. The authors indicate the need to replicate and expand the examination of critical windows for exposure (see section "Immunologic Effects" below).

In summary, except for the studies described above, there are no studies on growth and development of animals after developmental exposure to TCE either prenatally or postnatally. The above studies indicate neurologic and immunologic effects of TCE exposure during development. However, they have limitations in design and interpretation. Further study of TCE is required to determine the types of effects, the lowest effect levels, and critical windows of development.

Neurologic Effects

TCE, like many other VOCs, inhibits functions of the CNS and possibly the peripheral nervous system. Acute effects in humans range from slight dizziness, fatigue, and headache to incoordination, anesthesia, and death. TCE was commonly used for decades in vapor concentrations of about 2,000 ppm as a surgical, dental, and obstetrical anesthetic (Pembleton 1974). Such use was discontinued in the late 1970s. Chloral hydrate, an obligate intermediate of TCE's oxidative metabolic pathway, remains one of the most widely used sedatives for dental, emergency medical, and imaging procedures for young chil-

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dren (Keengwe et al. 1999). The magnitude of CNS depression induced by chloral hydrate and TCE depends on the administered dose and on the target organ (brain) dose. CNS inhibitory effects diminish and disappear as TCE is metabolized and it and its metabolites are eliminated from the body. It should be recognized that trichloroethanol, an end metabolite of the oxidation pathway, depresses the CNS. TCE's narcotic effects are generally considered to be reversible. Irreversible (neurotoxic) effects, however, have been reported in human populations exposed for years to concentrations of TCE and other organic solvents high enough to produce clinically significant CNS symptoms (Evans and Balster 1991; ATSDR 1997b; Bruckner et al. 2008). There is concern that exposures to lower concentrations may also pose a risk of residual neurotoxic effects (EPA 2001; NRC 2006).

TCE and other VOCs are intentionally inhaled for their euphoric and intoxicating effects. TCE and other solvents may be abused for years and result in malnutrition, cachexia, and residual damage of the brain and other organs; chronic neurologic and neuropsychologic sequelae have long been recognized. Rosenberg et al. (2002), for example, reported that a group of solvent abusers did significantly worse on tests of working memory and executive cognitive function than did alcoholics and cocaine addicts. A much higher percentage of solvent users had structural abnormalities in subcortical regions of the brain, as visualized by magnetic resonance imaging. They also exhibited moderate to severe diffuse abnormalities of cerebral white matter, a condition termed white-matter dementia. Inhalant abuse is the extreme form of TCE exposure, in that participants repeatedly subject themselves to vapor concentrations high enough to produce narcosis.

Occupational exposures to TCE often involve inhalation of relatively high concentrations for years. Usual exposure concentrations are much lower than those experienced by solvent abusers but substantially higher than encountered environmentally. Several studies of human subjects have been conducted to establish thresholds below which inhalation of TCE in the workplace will not impair motor or cognitive functions (ATSDR 1997b). Those studies have yielded surprisingly similar quantitative findings. Vernon and Ferguson (1969) exposed eight men to TCE at 0, 100, 300, and 1,000 ppm for 2 h. The highest concentration adversely affected performance on three of six standardized visual-motor tests; no significant decrements were found in response to the lower exposures. Stewart et al. (1970) measured a number of indexes of motor function in humans who inhaled TCE at 100 or 200 ppm for up to 7 h on 5 consecutive days. No decrements in performance were found, but some subjects described mild fatigue and sleepiness during their 4th and 5th days of inhaling TCE at 200 ppm. There were no significant differences in standardized achievement-test scores and self-reporting scales between controls and subjects who inhaled 100 ppm 6 h/day on 5 consecutive days (Triebig et al. 1977). Results of such studies served as the primary basis for the current occupational threshold limit value of 10 ppm and the short-term exposure limit of 25 ppm for TCE (ACGIH 2008). Those values were adopted in recognition that exercise enhances VOCs' systemic uptake and CNS effects.

There have been a number of reports of different neurophysiologic and neuropsychologic effects of TCE in workers after short-term and long-term exposure (ATSDR 1997b; NRC 2006). Acute exposures to vapor at 500 ppm and higher result in dose-dependent signs of intoxication. Those effects are usually reversible, although there have been occasional cases of residual nerve dysfunction in persons overcome by a single high exposure (Feldman et al. 1985; Leandri et al. 1995). The patient described by Leandri et al. exhibited trigeminal nerve damage up to 4 months after exposure. Effects of repeated long-term exposure include memory loss, mood swings, impairment of cognitive function, and olfactory and trigeminal neuropathy. In most instances, TCE concentrations were not known, and many of the study subjects were exposed to solvent mixtures. A few investigations measured vapor concentrations in the workplace. Workers chronically exposed at 38-172 ppm described symptoms of dizziness, headache, nausea, and sleepiness, but trigeminal nerve dysfunction was not apparent (El Ghawabi et al. 1973). Albee et al. (2006) recently found no change in trigeminal nerve evoked potentials in rats inhaling TCE at up to 2,400 ppm over 13 weeks. Ruijten et al. (1991) found a change in one of two indexes of trigeminal nerve impairment in 31 printing workers exposed to TCE at 35-80 ppm for an average of 16 years. No impairment of motor or autonomic nerves was found.

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Feldman et al. (1992) measured prolonged latency in the blink reflex, which is indicative of trigeminal nerve impairment, in two metal degreasers heavily exposed to TCE for 7 and 16 years. Ruijten et al. (1991) found slight reductions in sensory nerve conduction velocity consistent with subclinical impairment of the peripheral nervous system. Rasmussen et al. (1993) found no disturbance of the trigeminal nerve but observed altered function of the olfactory nerve in 99 metal degreasers exposed to "high" concentrations of solvents (primarily TCE) for an average of 11 years; they also described dose-dependent increases in motor dyscoordination in the degreasers.

A substantial number of neurotoxicity studies of TCE of acute and intermediate duration have been conducted in rats. CNS-depressant effects in the animals appear to be similar to those in humans and generally occur at higher exposure concentrations (ATSDR 1997b). That may be attributable in part to the availability of less sensitive measures of CNS depression in rodents. Bushnell and Oshiro (2000) found that inhalation of TCE at 2,000 or 2,400 ppm for 9 days reduced performance of rats on a sustained-attention task. Performance progressively improved (tolerance developed) during the protocol. Oshiro et al. (2004) then reported that inhalation of TCE at 1,600 or 2,400 ppm 6 h/day on 20 consecutive days did not impair later learning of a sustained-attention task. Inhalation at up to 1,500 ppm 16 h/day 5 days/week for 18 weeks increased latency in a visual-discrimination task but had no influence on spontaneous activity, grip strength, coordinated movement, or peripheral-nerve conduction time (Kulig 1987). Latency in a visual-discrimination task improved progressively in the 500-ppm and 1,500-ppm groups.

Auditory deficits in the midfrequency tone range have been observed in several strains of rats in response to inhalation of high concentrations of TCE (NRC 2006). Crofton and Zhao (1993), for example, described the onset of hearing loss after the fifth daily 6-h exposure at 4,000 ppm. It persisted for up to 14 weeks after exposure. The LOAEL in the study was 2,400 ppm. Histopathologic examination of rats that inhaled 4,000 ppm 6 h/day for 5 days revealed a loss of spiral ganglion cells in the middle turn of the cochlea and an inconsistent loss of hair cells (Fletcher et al. 1998). Recently, Albee et al. (2006) found focal loss of hair cells in the upper basal turn of the cochlea of rats that inhaled TCE at 2,500 ppm but not 800 ppm for 6 h/day 5 days/week for up to 13 weeks. Occupational exposures to such solvents as toluene and styrene have resulted in evidence of some hearing loss (Hodgkinson and Prasher 2006). That outcome has apparently not been assessed in groups exposed to TCE vapor at high concentrations. Kilburn (1999) reported an effect on the vestibulo-oculomotor system (balance) in a study of 150 jet-engine repairmen subjected to metal dusts and solvents, including TCE.

There have been some accounts of neurologic effects in animals caused by relatively low doses of TCE. Changes in visual evoked potentials were described in rabbits exposed repeatedly to TCE at 350 ppm over 12 weeks (Blain et al. 1992). Reduced exploratory and social behavior was seen in rats after weeks of daily 6- to 7-h exposures to TCE vapor concentrations as low as 100 ppm. Silverman and Williams (1975) did not use objective measurement techniques in their early study but merely observed the animals. Rats inhaling TCE at 50, 100, or 300 ppm for 8 h/day 5 days/week for 6 weeks exhibited altered sleep patterns; the effects were not dose-dependent (Arito et al. 1994). Decreased wakefulness during and after exposure was observed in the 50- and 100-ppm groups, respectively. The biologic or toxicologic significance of that effect is not apparent, but the Agency for Toxic Substances and Disease Registry (ATSDR) and the U.S. Environmental Protection Agency (EPA) each chose to use 50 ppm as the LOAEL with which to determine human exposure guidelines. ATSDR used an interspecies uncertainty factor of 3; EPA did not account for interspecies kinetic differences in its calculations. As described in Chapter 3, systemic uptake of inhaled VOCs is significantly greater in rodents than in humans. Physiologically based pharmacokinetic modeling has shown that higher blood concentrations are attained in rats during the initial hours of an 8-h exposure to TCE at 10 and 100 ppm (Bruckner et al. 2004).

Some investigations of potential cognitive effects of relatively low concentrations of TCE in rodents showed few adverse effects. Grandjean (1963) observed that inhalation of TCE at 800 ppm reduced swimming time in rats but produced no change in shuttle box or maze performance. Bushnell (1997) assessed the influence of a series of vapor concentrations on rats' response times to obtain a food reward; the NOAEL was 800 ppm. Albee et al. (1997) did not find alteration of flash-evoked potentials in rats inhaling 250 ppm. Waseem et al. (2001) stated that daily inhalation by rats of TCE at 376 ppm over 180

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days or consumption of TCE at 350, 700, or 1,400 ppm in water did not alter acquisition of a conditioned shock-avoidance response (cognition) but did enhance spontaneous motor activity. Similar findings in rats were described by Grandjean (1960) after acute 11- to 14-h inhalation exposures at 200 and 800 ppm. Those activity increases reflect the initial stimulant phase of action of CNS depressants.

A few studies of TCE exposure in drinking water at about 30 mg/kg per day during pregnancy and lactation reported increased activity, reduced 2-deoxyglucose uptake in brain, and reduced hippocampal myelin (Taylor et al. 1985; Noland-Gerbec et al. 1986; Isaacson and Taylor 1989). An additional study (Isaacson et al. 1990) reported learning deficits and reduced hippocampal myelin in rats exposed as weanlings and adults. All those studies were from the same group, involved small numbers of animals, and require confirmation (see section "Growth and Development" above).

Cancer

Standard practice in 2-year bioassays is to perform gross and often microscopic pathologic investigations of all organ systems in animals, including animals that die early. In general, an animal model is deemed relevant to establish the relative importance of the types of cancer, if any, that exposure to a given chemical at specific doses over a lifetime would be likely to elicit. In that context, animal TCE cancer bioassays cited previously did not show causality for brain cancer or other neurologic cancers.

Immunologic Effects

TCE has been reported to produce several forms of immunotoxicity, including the ability to act as a skin sensitizer, to exacerbate respiratory hypersensitivity (allergic asthma), to produce immunosuppression, and to influence autoimmune diseases. Autoimmunity has been by far the most studied, and will be given the most attention here.

Allergic Sensitization

There have been many reports that workers exposed to TCE often show a severe irritating contact dermatitis manifested by a rash on the extremities, face, neck, or trunk with or without fever (Kamijima et al. 2007). It is sometimes referred to as severe generalized dermatitis, but it is unclear whether it has an immunologic etiology. Recently, a study conducted in workers at an electronic-element and metal-plating production plant in Guangdong Province, China, suggested an association with TCE-induced severe generalized dermatitis and the HLA-B*1301 allele (Li et al. 2007). HLA alleles, known to be involved in governing immune recognition, are often reported to be associated with immune diseases. The evidence that TCE causes allergic contact dermatitis (skin allergy) comes primarily from a study by Tang et al. (2002) that used a modified guinea pig maximization test. TCE molecules themselves are too small to be antigenic and would need to bind covalently with skin proteins to elicit an immune response.

There is no evidence that TCE can directly induce asthma, but data suggest that it can modulate asthma. Acute intraperitoneal administration of TCE to rats at 0.1mL/kg enhanced the production of several regulatory cytokines, including interleukin-4 (IL-4), and induced histamine release from basophils in animals previously immunized with a protein allergen (Seo et al. 2008). IL-4 and histamine are involved in the development of allergic asthma. The authors showed similar effects by treating cells in vitro with TCE from animals immunized with a protein allergen. Thus, unlike the Tang et al. (2002) study, which suggested that TCE directly causes allergic contact dermatitis, the studies by Seo et al. (2008) suggest that TCE may act as an adjuvant in enhancing allergic respiratory disease. Other studies have shown that VOCs may modulate immune cell types to favor induction of allergic responses in young children (Lehmann et al. 2001). It is worth noting that a number of indoor and outdoor air pollutants are believed to

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exacerbate asthma, particularly in children (Selgrade et al. 2006). Further studies are needed to clarify those observations and determine whether TCE can induce or modulate allergic diseases.

Immunosuppression

That TCE can cause immunosuppression was first suggested on the basis of experimental-animal studies. Sanders et al. (1982) showed that mice exposed to TCE in drinking water for 4 or 6 months had deficiencies in their ability to mount normal immune responses. At a concentration as low as 100 mg/L (about 22 mg/kg per day), cell-mediated immunity and bone-marrow stem-cell colonization were inhibited. Wright et al. (1991) were able to confirm many of those findings in mice and rats treated with TCE by intraperitoneal injection. Peden-Adams et al. (2006) recently reported that mice exposed prenatally and postnatally to TCE are immunosuppressed at concentrations as low as 1.4 ppm in drinking water from gestation day 0 through the age of 3 or 8 weeks. Developmental immunotoxicity was manifested by suppression of antibody responses and decreases in B-cell numbers with a concomitant increase in delayed hypersensitivity responses and T-cell numbers. The shift in immune function would favor the development of infections from extracellular bacteria, such as streptococci and klebsiellae. The authors indicated that their data were preliminary and needed to be replicated (see section "Growth and Development").

Kaneko et al. (2000) reported that TCE suppressed immune functions in MRL-*lpr/lpr* mice after inhalation exposure to vapor at 1,000 or 2,000 ppm for 4 h/day for up to 8 weeks. The MRL-*lpr/lpr* mouse is genetically predisposed to develop systemic lupus erythematosus.

Epidemiologic studies of TCE exposure and immunosuppression have been few. Byers et al. (1988) found increased concentrations of $CD4^+$ and $CD8^+$ T cells in a population with chronic domestic exposure to solvent-contaminated drinking water. Iavicoli et al. (2005) investigated the association between serum concentrations of IL-2, IL-4, and interferon gamma (IFN-γ) in workers exposed to TCE (mean urinary trichloroacetic acid concentration, 13.3 mg/g of creatinine). Serum concentrations of IL-2 and IFN-γ were increased, and that of IL-4 was reduced. Without additional immune tests, interpretation of variations in serum cytokines is currently not possible. Taken together, studies seem to be consistent in supporting the ability of TCE to suppress the immune system, at least in experimental animals. It should also be noted that the immunosuppressive effects seen in experimental animals generally occur at doses at which hepatic toxicity can be observed.

Autoimmunity

The MRL+/+ mouse model has been used historically to study TCE-induced autoimmunity. It is one of several mouse strains that have a mutation that results in the spontaneous development of systemic lupus erythematosus (SLE). The MLR+/+ strain was derived from the MRL-*lpr/lpr* mouse. The latter has a Fas mutation, a key protein responsible for cellular apoptosis, which influences the development of lupus early in life (50% mortality by the age of 6 months). The MLR+/+ mice lack the Fas mutation and develop the disease much slower (50% mortality within 17 months). Activated $CD4^+$ T cells and regulatory cytokines (such as IFN-γ) play a key role in the development of SLE in MLR+/+ mice. Khan et al. (1995) showed that TCE accelerates the autoimmune disease process in MLR+/+ mice. Numerous studies have since examined the disease characteristics and mechanisms of action.

Several mechanisms, not at all mutually exclusive, that have been proposed for TCE-induced autoimmunity are consistent with current understanding of the etiology of autoimmune disease. It has been suggested that TCE reactive metabolites, such as dichloroacetyl chloride (Khan et al. 1995, 2001) and lipid peroxidation-derived aldehydes, which form after TCE exposure (Wang et al. 2008), covalently bind to host proteins (Wang et al. 2007) and become immunogenic. Those protein adducts act as neoantigens and result in recognition by and activation of autoreactive T cells and autoantibody production. In further support of the hypothesis, Cai et al. (2007) were able to produce an immune response to adducts

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derived from TCE reactive metabolites after immunization in mice, and Wang et al. (2008) activated T cells in vitro after incubation with the protein adducts. Consistently with the formation of TCE metabolites that form protein adducts, Griffin et al. (2000a) prevented adduct formation and reversed, at least in part, the autoimmune effects in TCE-treated MRL+/+ mice by cotreatment with diallyl sulfide, an inhibitor of CYP2E1 that prevents TCE metabolism.

TCE treatment of MRL+/+ mice also has been suggested to stimulate $CD4^+$ T cells directly (Gilbert et al. 1999). The activated $CD4^+$ T cells develop a surface antigen, referred to as CD44 (Griffin et al. 2000b), that is involved in cell adhesion and is highly expressed in MRL-*lpr/lpr* mice. Treatment of MLR+/+ mice with trichloroacetaldehyde hydrate or trichloroacetic acid, major TCE metabolites, also activated CD4 T cells (Blossom et al. 2004). Consistently with the ability of CYP2E1 inhibition to reverse the autoimmune effects (Griffin et al. 2000a), the activated cells are less susceptible to a form of cellular apoptosis, referred to as activation-induced cell death, that is observed in many autoimmune diseases. TCE-mediated defects of activation-induced cell death were recently found to be associated with metalloproteinase 7, which later facilitated FasL, a receptor involved in apoptosis (Blossom and Gilbert 2006). The T cells activated by the protein adducts are believed to represent predominantly a Th1 phenotype, rather than Th2, inasmuch as they produced higher concentrations of IFN-γ, a Th1 cytokine, and lower concentrations of IL-4, a Th2 cytokine. Th1 cytokines are usually associated with systemic autoimmune diseases. Gilbert et al. (1999, 2004) also provided evidence that trichloroacetaldehyde hydrate can activate T cells through the formation of a Schiff base. Schiff-base-forming structures, such as aldehydes and ketones, can substitute for physiologic donors of carbonyl groups and directly activate CD4 cells without engaging the T-cell receptor (Rhodes et al. 1995).

The chronic effects of TCE exposure in MLR+/+ mice have been addressed in several studies. Griffin et al. (2000c) exposed MLR+/+ mice to TCE at 0.1, 0.5, or 2.5 mg/mL in drinking water (21, 100, or 400 mg/kg) for 4 or 32 weeks and showed $CD4^+$ T-cell activation and induction of autoimmune hepatitis at all doses. Cai et al. (2008) exposed mice to TCE at 0.5 mg/mL in drinking water for up to 48 weeks. In addition to increases antinuclear autoantibody titers, lymphocyte infiltration and immunoglobulin deposits were found in the liver, pancreas, lungs, and kidneys (including glomeruli); this was consistent with SLE or an SLE-like disease. Blossom et al. (2007) treated MLR+/+ mice with trichloroacetaldehyde hydrate at 0.1, 0.3, or 0.9 mg/mL (about 13, 49, or 143 mg/kg per day) in drinking water for 40 weeks. Long-term exposure promoted alopecia and skin inflammation. The lesions did not appear similar to the cutaneous lupus seen in older MLR mice or the skin conditions in patients with systemic scleroderma; rather, they may have been associated with dermal infiltration of activated T cells.

Taken together, the experimental studies suggest two mechanisms, not mutually exclusive, by which TCE modulates autoimmune disease. The first involves TCE reactive metabolites that covalently bind to host protein to produce neoantigens that stimulate the formation of autoreactive immune cells. The second involves activation of Th1 cells nonspecifically by TCE metabolites, which also leads eventually to the formation of autoreactive immune cells. Both processes, like autoimmune diseases in general, involve cellular apoptosis. The latter is a general mechanism that may be relevant to a variety of autoimmune diseases, whereas the former may be more specific to particular diseases (such as lupus).

PERCHLOROETHYLENE

Data on the toxicity of PCE were summarized in a 1985 health assessment by EPA (1985) and an addendum issued in 1986 (EPA 1986). The California Environmental Protection Agency published a public-health goal for PCE in drinking water (CalEPA 2001) that included a brief review of toxicity data. ATSDR (1997c) also published a toxicologic profile of PCE, and a draft neurotoxicity assessment was available from EPA (2003). Literature reviews were available in particular subject areas (e.g., Beliles 2002; Klaunig et al. 2003; Wernke and Schell 2004). Such references were relied on for defining the body of literature available on PCE; in addition, a literature search was done to determine whether any relevant new publications were available. Conclusions drawn for the present report were based on a review of the

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body of available literature. The data are presented below by organ system, and toxic effects are considered separately from carcinogenic effects.

Hepatic Effects

Toxicity

PCE, like TCE, has a limited ability to cause acute, subacute, or chronic hepatic injury in rodents. Klaassen and Plaa (1966) assessed the acute cytotoxicity of PCE, TCE, and several other halocarbons in male Swiss-Webster mice given each chemical in a single intraperitoneal injection. PCE was a slightly less potent hepatotoxicant than TCE. A lethal dose of PCE was required to produce a substantail increase in serum alanine aminotransferase activity. Recently, Philip et al. (2007) reported that male Swiss-Webster mice given PCE at 150 mg/kg by aqueous gavage exhibited a transient increase in serum alanine aminotransferase activity. Higher alanine aminotransferase concentrations were manifested at 500 and 1,000 mg/kg. The extent of injury regressed substantially over a 30-day dosing period, apparently because of the onset of tissue repair and PCE's inhibition of its own oxidative metabolism. Buben and O'Flaherty (1985) saw modest increases over controls in serum alanine aminotransferase, liver weight, and hepatic triglycerides in male Swiss-Cox mice dosed with PCE at 500-2,000 mg/kg per day for 6 weeks by corn-oil gavage; the lack of dose dependence reflected saturation of metabolic activation in this dosage range. Hayes et al. (1986) found no consistent dose-related effects on any hematologic or clinical-chemistry measure in male or female rats that ingested PCE at about 14, 400, or 1,440 mg/kg per day for 90 days. Rats may be less susceptible than mice, although the absence of hepatotoxicity in rats in this instance can also be attributed to differences in oral-exposure regimens. Ingestion of a bolus dose of PCE will result in a high tissue dose that exceeds the capacity of the liver's defense and repair mechanisms. Consumption of the total dose in relatively small, divided doses might not exceed such a cytotoxicity threshold.

PCE-induced hepatic injury is believed to be a consequence of oxidative metabolism of PCE (Lash and Parker 2001). The PCE oxidative pathway is described in Chapter 3 (see section on metabolic activation and inactivation of TCE and PCE). PCE is more poorly metabolized by cytochrome P-450s than TCE, but two additional intermediate metabolites of PCE also contribute to its hepatocytotoxicity: the initial oxidation product, PCE oxide (epoxide), and one of its convertants, trichloroacetyl chloride. The latter is transformed to trichloroacetic acid, the major metabolite of PCE. Some trichloroacetic acid can be dechlorinated to form dichloroacetic acid. Trichloroacetic acid and dichloroacetic acid are also products of TCE biotransformation. As described earlier, trichloroacetic acid is primarily responsible for activation of the nuclear receptor PPARα, which stimulates peroxisomal enzymes and selected cytochrome P-450s involved in lipid metabolism. That results in peroxisome proliferation, which generates reactive oxygen moieties that can cause lipid peroxidation, cellular injury, and altered expression of cell-signaling proteins (Bull 2000). Lash et al. (2007) recently demonstrated that cytochrome P-450 inhibition resulted in reduced injury of hepatocytes isolated from male F344 rats and exposed to PCE. Glutathione depletion increased cellular injury, apparently because of a shift from glutathione conjugation to the oxidative metabolism of PCE.

Humans should be less susceptible to hepatic injury by PCE than rodents because of lower internal and target-organ doses of the parent compound and its bioactive metabolites. As described in Chapter 3, rats achieve a substantially higher internal dose of PCE than humans on inhaling it. Volkel et al. (1998) subjected rats and people to identical PCE inhalation regimens. Blood trichloroacetic acid concentrations were 3- to 10-times higher in the rats. Dichloroacetic acid was not detectable in human urine, but substantial amounts were found in rat urine. A study of the urinary excretion of total trichloro-metabolites by PCE-exposed workers led Ohtsuki et al. (1983) to conclude that the capacity of men to metabolize PCE was rather rather low. Lash and Parker (2001) noted that saturation of PCE metabolism occurred at lower doses in humans than in rodents. That implies that humans have lower capacity to form biologically active metabolites from moderate to high PCE doses. The difference is reflected in the finding of much

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lower concentrations of protein adducts in the blood of humans than in the blood of rats subjected to equivalent PCE inhalation exposures (Pahler et al. 1999). Stewart et al. (1977) found no evidence of hepatotoxicity in six male and six female volunteers exposed randomly to PCE at 0, 25, or 100 ppm 5.5 h/day 5 days/week for 11 weeks. Serum alanine aminotransferase activity was not increased in 22 dry cleaners examined in Belgium (Lauwerys et al. 1983). A research group in Italy studied 141 employees exposed to PCE in small laundries and dry-cleaning shops (Gennari et al. 1992); no worker exhibited clinical signs of hepatic dysfunction or abnormal serum enzyme concentrations, although there did appear to be an increase in one isozyme of γ-glutamyltransferase, which was said to be associated with hepatobiliary impairment. Another investigation of dry cleaners failed to reveal increases in serum enzyme concentrations but did show mild to moderate changes in hepatic parenchyma revealed by ultrasonography (Brodkin et al. 1995). Considerable experience in occupational settings demonstrates that humans, like rodents, may develop mild but reversible hepatic injury on exposure to high concentrations (ATSDR 1997b).

Cancer

Exposure to PCE by inhalation (NTP 1986a) and by oral gavage (NCI 1977) has shown increases in liver cancer in $B6C3F_1$ mice (Table 4-1). Inhalation exposure of 50 $B6C3F_1$ mice of each sex at 0, 100, and 200 ppm 6 h/day 5 days/week for 103 weeks caused increased incidence of hepatocellular neoplasms (adenomas and carcinomas combined) in males and females. The incidence in males was 17 of 49, 31 of 49, and 41 of 50, respectively; in females, it was 4 of 48, 17 of 50, and 38 of 50, respectively. As also shown in Table 4-1, exposure of male $B6C3F_1$ mice to PCE at 536 and 1,072 mg/kg per day and of female mice at 386 and 722 mg/kg per day in corn oil with epichlorohydrin stabilizer by oral gavage yielded significant increases in hepatocellular carcinomas ($P < 0.001$). Thus, there is clear evidence of hepatic carcinogenicity in $B6C3F_1$ mice related to PCE exposure.

No hepatic-cancer effects were seen in F344/N rats exposed by inhalation to PCE at 200 and 400 ppm for 103 weeks (NTP 1986a).

Trichloroacetic acid is also a metabolite of PCE. As discussed in detail in the preceding section on TCE cancer bioassays, trichloroacetic acid induces peroxisome proliferation in $B6C3F_1$ mouse liver but not in rat liver. That difference should be taken into account, as discussed in greater detail in the preceding section, in considering the relevance of mouse hepatocellular tumors for humans.

As shown in Table 4-2, gavage studies to determine carcinogenicity in Osborne Mendel rats (NCI 1977) were judged inadequate because of early mortality when PCE-induced toxic nephropathy reduced survival of dosed rats. There were many early deaths, so those results precluded conclusions regarding carcinogenicity of PCE in the rats.

Renal Effects

Toxicity

PCE is somewhat more nephrotoxic in mice and rats than TCE, but high, subchronic oral bolus dosing with PCE is required to affect the kidneys adversely. Jonker et al. (1996), for example, gave female Wistar rats TCE at 500 or 600 mg/kg per day by corn-oil gavage for 32 consecutive days. PCE elicited doubling of urinary protein and activities of several enzymes released from injured renal proximal tubule cells. TCE produced slight increases in just two of the enzymes. Coadministration of TCE and PCE resulted in additive nephrotoxicity. Philip et al. (2007) recently failed to see morphologic changes in the kidneys of male Swiss-Webster mice given PCE at 150, 500, or 1,500 mg/kg per day by aqueous gavage for 30 days. Green et al. (1990) gavaged male F344 rats with PCE at 1,500 mg/kg per day in corn oil for 42 days. There were increases in urine volume and urinary enzyme activities that were indicative of

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TABLE 4-1 Animal Cancer Studies of PCE with Positive Outcomes

Species	Strain	Dose or Concentration	Route	Timing and Duration	Outcomes	LOAEL	References
Mouse	$B6C3F_1$	0, 100, 200 ppm	Inhalation	6 h/day 5 days/week, 103 weeks	Hepatocellular adenoma in males; hepatocellular carcinoma in males, females	100 ppm	NTP 1986a
Mouse	$B6C3F_1$	Males: 0, 536, 1,072 mg/kg per day; females: 0, 386, 722 mg/kg per day; epichlorohydrin stabilizer	Oral gavage (corn oil)	5 days/week, 78 weeks, observed to 90 weeks	Hepatocellular carcinoma in males, females	536 mg/kg per day (males); 386 mg/kg per day (females)	NCI 1977
Rat	F344/N	0, 200, 400 ppm	Inhalation	6 h/day 5 days/week, 103 weeks	Stage 3 mononuclear cell leukemia;[a] rare renal tubular adenoma, adenocarcinoma in males	200 ppm (males, females)	NTP 1986a; Mennear et al. 1986

[a]Mononuclear-cell leukemia is common in aging F344 rats.

TABLE 4-2 Animal Cancer Studies of PCE Determined to be Negative, Inadequate, or Incomplete

Species	Strain	Dose or Concentration	Route	Timing and Duration	Outcomes	Comment	NOAEL	Reference
Rat	Osborne Mendel	Males, 471, 941 mg/kg per day; females, 474, 949 mg/kg per day	Oral gavage (corn oil)	78 weeks	Early mortality due to PCE-induced toxic nephropathy	Inadequate study	—	NCI 1977
Rat	Sprague-Dawley	0, 300, 600 ppm, 6 h/day, 5 days/week	Inhalation	52 weeks, then held another 12 mo	Hematologic examinations and tumor outcomes negative	Short duration of exposure; unpublished	600 ppm	Rampy et al. 1978
Rat	Sprague-Dawley	0, 500 mg/kg per day	Oral gavage (olive oil)	4-5 days/week, 104 weeks	No increase in total and malignant tumors at 141 weeks	Negative study	500 mg/kg per day	Maltoni et al. 1986
Rat	Long-Evans Sherman Wistar F344	—	Oral gavage	In-life studies completed; overall findings unpublished	Study judged "inadequate," no final report available	Inadequate study	—	NTP 1986a
Mouse	Ha:ICR Swiss	1st application, 163.0 mg; 2nd application, 54.0 mg	Skin	1st application, 229 days to papilloma; 2nd application: 0 papillomas	1st application, 4/7 mice with papillomas/total papillomas; 2nd application, 0	Negative study; $P > 0.05$	—	Van Duuren et al. 1979

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mild renal proximal tubular-cell damage. Histopathologic examination revealed the presence of hyaline droplet accumulation and some regeneration in the animals' proximal tubules. Ingestion of daily doses of PCE estimated at 14, 400, or 1,400 mg/kg in drinking water for 90 days failed to produce renal damage in male or female Sprague-Dawley-derived CD rats (Hayes et al. 1986). Thus, ingestion of divided doses of PCE in water over the course of the day is much less nephrotoxic in rodents than ingestion of the total dose once a day.

Subchronic and chronic inhalation of PCE has resulted in limited evidence of nephrotoxicity in rodents. Exposure of both sexes of F344 rats and $B6C3F_1$ mice to PCE at 400 ppm 6 h/day for 28 days failed to increase renal weights or produce histopathologic changes. Tinston (1995) reported mild, progressive glomerulonephropathy and increased pleomorphism of proximal tubular nuclei in male but not female rats that inhaled PCE at 1,000 ppm for up to 19 weeks. Nephropathy was seen in rats and mice chronically given high oral bolus doses of PCE in corn oil (NCI 1977). Karyomegaly occurred in renal tubules of male and female $B6C3F_1$ mice exposed to PCE at 200-1,600 ppm by inhalation for 13 weeks (NTP 1986a); the NOAEL in mice was 100 ppm. Renal lesions were not seen in F344 rats exposed to PCE at 1,600 ppm. Dose-dependent karyomegaly was observed in each sex of rats exposed to PCE at 200 or 400 ppm and mice exposed at 100 and 200 ppm chronically (NTP 1986a); there were also low incidences of renal proximal tubular-cell hyperplasia in the male rats.

The metabolism and mode of nephrotoxicity of PCE and TCE appear to be quite similar, although PCE and its metabolites are somewhat more potent. Renal effects of both halocarbons are due primarily to metabolites formed via the glutathione conjugation pathway (Lash and Parker 2001). The sites, enzymes, and products associated with PCE biotransformation are almost identical with those associated with TCE. (The TCE and PCE glutathione conjugation pathways were described earlier in Chapter 3.) The primary difference is that *S*-(1,2,2-trichlorovinyl)glutathione (TCVG) and *S*-(1,2,2-trichlorovinyl)-L-cysteine (TCVC) are produced from PCE, and DCVG and DCVC from TCE. TCVC can be detoxified by acetylation or cleaved by renal cytosolic and mitochondrial β-lyases to trichlorothioketene, which loses a chloride ion to form dichlorothioketene. The latter is a very reactive moiety that binds to cellular proteins and DNA. TCVC, like DCVC, can be enzymatically oxidized to form the very reactive *S*-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide (TCVCS) (Krause et al. 2003). TCVCS was shown to be more nephorotoxic than TCVC in male Sprague-Dawley rats on intraperitoneal injection (Elfarra and Krause 2007). TCVC caused more pronounced necrosis of renal proximal tubular cells in male Wistar rats than did DCVC after intravenous injection (Birner et al. 1997). Lash et al. (2002) similarly found that PCE and TCVG were more toxic than TCE and DCVG to renal cortical cells from F344 rats in vitro. Cells from male rats were more sensitive than cells from females to PCE-induced and TCVG-induced mitochondrial state 3 respiratory inhibition and cytotoxicity. Isolated rat hepatocytes and their mitochondria were unaffected by PCE and TCVC. Increased glutathione concentrations increased TCE-induced and PCE-induced cytotoxicity in suspensions of rat renal cortical cells but not hepatocytes (Lash et al. 2007). In summary, PCE's glutathione-pathway metabolites are more reactive and cytotoxic in the kidney than are TCE's glutathione metabolites. PCE cytotoxicity is both sex-dependent and tissue-dependent.

Occupational exposures to PCE vapor have led to several reports of mild renal tubular damage (ATSDR 1997b). Employees of dry-cleaning shops have been the subjects of a number of investigations. Increased concentrations of urinary lysozyme or increased β-glucuronidase activity was described in dry cleaners exposed to PCE at average concentrations of 10 ppm (Franchini et al. 1983) and 23 ppm (Vyskocil et al. 1990) for 9-14 years. In a more comprehensive study of renal function, a number of urinary indexes indicative of early glomerular and tubular changes were increased over controls in 50 dry cleaners who inhaled PCE at an average concentration of 15 ppm for 10 years (Mutti et al. 1992). There was a lack of association between the extent of the changes and the intensity and duration of exposure. Verplanke et al. (1999) monitored several indexes of tubular and glomerular function in Dutch dry-cleaning workers but found an increase only in retinol-binding protein in their urine. Other groups of investigators have failed to find evidence of renal effects in such populations. A laboratory study of 10 male and 10 female adults who inhaled PCE at up to 150 ppm for as long as 7.5 h/day for 5 days did not show changes from pre-exposure baseline urinary and blood urea nitrogen concentrations (Stewart et al. 1981). Hake and

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Stewart (1977) described a dry cleaner who was found unconscious in a pool of PCE, where he had been for an estimated 12 h. Laboratory tests revealed hematuria and proteinuria that lasted for 10 and 20 days, respectively. Mild hepatic damage was revealed by transient increases in serum enzymes. On the basis of the foregoing human experiences, PCE has limited ability to cause diffuse changes along the nephron, although extremely high exposures can lead to pronounced changes.

Cancer

No renal carcinomas were observed in B6C3F$_1$ mice exposed to PCE at 0, 100, and 200 ppm for 103 weeks (NTP 1986a); dose-related karyomegaly was found in both males and females, but it was not accompanied by tubular-cell hyperplasia as it was in rats (Table 4-1).

F344/N rats develop nephrologic changes as a normal condition of ageing. Both sexes showed renal tubular-cell karyomagaly and males renal tubular-cell hyperplasia after exposure to PCE at 200 and 400 ppm for 103 weeks (NTP 1986a). That effect has been seen in other strains of rats exposed to chlorinated ethylenes, so it is not necessarily specific to PCE. Renal tubular-cell adenomas and adenocarcinomas were detected in male, but not female, rats. The incidence of renal neoplasm in the males was 1 of 49 controls, 3 of 49 exposed at 200 ppm, and 4 of 49 exposed at 400 ppm. Even though the results were not statistically significant, it was noted that those particular tumors are rare in F344/N male rats, so they were believed to have been caused by PCE exposure.

Pulmonary Effects

Toxicity

Little information was available on the pulmonary toxicity of PCE in laboratory animals or humans. Epithelial degeneration was observed in mice that inhaled PCE at 300 ppm 6 h/day for 5 days (Aoki et al. 1994). That effect was more severe in the olfactory than in the respiratory mucosa. Mice exposed to PCE at 50 ppm for 3 h were more susceptible to two strains of inhaled bacteria than controls (Aranyi et al. 1986). It was hypothesized that the susceptibility occurred because PCE inhibited alveolar macrophage activity. Intermittent inhalation of of PCE at 1,600 ppm for 13 weeks produced congestion in the lungs of rats (NTP 1986a). The 800-ppm vapor concentration did not have that effect. Pulmonary congestion was seen in mice that inhaled PCE at 100 ppm or greater in the 103-week phase of the cancer bioassay. There was not an increased incidence of lung tumors in the mice or rats. The reason for the apparent lack of significant pulmonary toxicity or carcinogenicity in rodents may have been the small amounts of the cytochrome P-450 isozymes that metabolically activate PCE. Although CYP2E1 is abundant in mouse lung, it does not appear to be active in PCE metabolism in rat (Hanioka et al. 1995) or human (White et al. 2001) cells, thereby inferring that CYP2E1 is unlikely to be a factor in metabolizing PCE in the rat or human lung. A number of studies of inhaled PCE have shown that vapor concentrations as low as about 200-300 ppm can cause mild irritation of the nasal passages of humans (ATSDR 1997b). Stewart et al. (1981) subjected four male volunteers to PCE at 0, 20, 100, and 150 ppm 7.5 h/day for 5 days. The subjects were exposed sequentially to each concentration for 1 week. Pulmonary-function measurements did not reveal any decrements. Pulmonary edema has been described in a person rendered unconscious by PCE fumes (Patel et al. 1973).

Cancer

No increases in lung proliferative lesions were seen in B6C3F$_1$ mice of either sex after inhalation of PCE at 100 or 200 ppm for 103 weeks, nor were lung neoplasms seen in male or female F344/N rats exposed at 200 or 400 ppm for 103 weeks (NTP 1986a).

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Genotoxicity

The genetic toxicity of PCE has been reviewed extensively by the California Environmental Protection Agency (CalEPA 1992), the International Agency for Research on Cancer (IARC 1995), and ATSDR (1997c). In general, studies have not yielded evidence of genotoxicity of PCE. Results in prokaryotic mutation assays (principally with *Salmonella typhimurium and Escherichia coli*) have been negative with and without S-9 rat liver microsomal metabolic activation. More recently, PCE was negative in an *S. typhimurium* tester strain competent for CYP2E1 metabolizing capacity (Emmert et al. 2006). Metabolites of PCE have been shown to be mutagenic in vitro. The minor PCE urinary metabolite glutathione conjugate TCVG is mutagenic in *S. typhimurium* TA 100 with renal cytosol metabolic activation (Vamvakas et al. 1987). TCVG, the precursor of the cysteine conjugate, was also mutagenic to *S. typhimurium* TA 100 with rat kidney microsomal metabolic activation (Vamvakas et al. 1989).

Reproductive Effects

Toxicity

Only two studies have addressed the potential for reproductive toxicity of PCE: a study by Beliles et al. (1980) and a two-generation study by Tinston (1995). In the Beliles et al. (1980) study, male rats and mice were exposed to PCE by inhalation at 100 and 500 ppm 7 h/day for 5 days. No effects on sperm structure were seen in rats, but in the 500-ppm group of mice, there was a significant increase in the incidence of abnormal sperm heads 4 weeks after exposure. The timing of the appearance of the effects after exposure suggests that spermatocyte or spermatogonia were most sensitive to exposure to PCE. The NOAEL was 100 ppm.

The two-generation study by Tinston (1995) involved exposure of male and female rats (Alpk:ApfSD) to PCE at 0, 100, 300, or 1,000 ppm 6 h/day 5 days/week for 11 weeks before mating and then daily during mating and through gestation to day 20. There was no exposure from gestation day 21 through postnatal day 6, and then exposure resumed. F_1 parents were selected on postnatal day 29, and exposure continued for at least 11 weeks before mating and then through mating, gestation, and lactation until the F_2 litters were weaned. Parental animals experienced CNS depression, decreased respiration at 300 and 1,000 ppm, decreased body weight at all concentrations during lactation, and nephrotoxicity at 1,000 ppm. Later growth in the 100-ppm and 300-ppm groups was similar to that in controls. There were reductions in live births, litter size, postnatal survival, and pup weight at 1,000 ppm. Pup kidney, liver, and testis weights were reduced at 300 and 1,000 ppm but not when adjusted for body weight. The NOAEL was considered to be 100 ppm.

Cancer

PCE has not been shown to cause testicular tumors in mice or rats in chronic carcinogenicity bioassays. The potential oncogenicity of PCE was evaluated in male and female F344 rats that inhaled PCE at 0, 200, or 400 ppm 6 h/day 5 days/week for 2 years (NTP 1986a). The overall incidence of Leydig cell tumors was 70%, 80%, and 82% in the 0-, 200-, and 400-ppm groups, respectively. Haseman et al. (1998) reported that NTP control F344 rats have an extremely high spontaneous incidence (89.1%) of Leydig cell tumors. F344 rats have therefore been replaced in the NTP bioassay program with Wistar Han rats. As discussed in the foregoing PCE reproductive-cancer section, Leydig cell tumors in F344 rats are believed to be irrelevant to humans.

In summary, the effects of PCE on sperm morphology and germ cells in rats and mice suggest an effect on male reproduction (Beliles et al. 1980; Tinston 1995), but more detailed studies are needed to clarify the effects and the relationship to magnitude of exposure. On the basis of the available studies, the

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LOAEL was 300 ppm for exposure 6 h/day 5 days/week for 11 weeks before mating and then daily during mating and through gestation to day 20. The NOAEL was 100 ppm. Leydig cell tumors reported in the chronic study (NTP 1986a) were discounted because of the high background rates of such tumors in F344 rats.

Developmental Effects

Pregnancy Outcomes

Several studies in rodents have focused on the potential for developmental toxicity of PCE. Schwetz et al. (1975) exposed pregnant mice and rats to PCE at 300 ppm on gestation days 6-15 and found maternal and developmental toxicity, including lowered weight of mice, subcutaneous edema in mouse fetuses, and increased resorption in rats. Beliles et al. (1980) found only minor changes in development in rats exposed to PCE at 300 ppm 7 h/day 5 days/week, either before mating and throughout gestation or only during gestation. In rabbits exposed at 500 ppm before or during gestation, there were no significant maternal or developmental effects.

Tepe et al. (1982) studied the effects of PCE exposure at 1,000 ppm in Long-Evans female rats before mating and during pregnancy or only during pregnancy to determine the more sensitive window. Increased relative maternal hepatic weight and reduced fetal body weight were seen after exposure to PCE at 1,000 ppm by inhalation during pregnancy. An increase in skeletal variations was seen in the group exposed before mating and during pregnancy, and soft-tissue variations (such as renal dysplasia) were seen more in the group exposed only during pregnancy.

Narotsky and Kavlock (1995) evaluated the effects of PCE at 0, 900, or 1,200 mg/kg per day administered orally by intubation on gestation days 6-19. There were no live pups in the 1,200-mg/kg group; maternal ataxia and reduced weight, fewer pups per litter, full litter resorptions, and microphthalmia or anophthalmia were seen at 900 mg/kg. Because of the high doses used and incomplete anatomic evaluation of pups, this study has little utility in hazard characterization.

More recently, Carney et al. (2006), using a standard prenatal developmental-toxicity study protocol (inhalation exposure 6 h/day 7 days/week on gestation days 6-20), reported reduced uterine and placental weights, reduced body weight, and reduced ossification in the thoracic vertebral centra in rats at PCE concentrations of 250 and 600 ppm and maternal toxicity at 600 ppm. The LOAEL for reduced fetal body weight was 250 ppm in this study. Reduced fetal body weight in the rat can be considered analogous to "small for gestational age" in humans.

An in vitro study by Saillenfait et al. (1995) reported concentration-dependent decreases in growth and differentiation indexes and increases in morphologic abnormalities in rat whole-embryo culture (gestation day 10) in a medium containing PCE at 3.5 mM. However, the relevance of the data to human risk assessment is questionable.

In summary, data from recent studies do not substantially alter the conclusions of EPA (1985), which were that data "do not indicate any significant teratogenic potential of PCE" and that other observed effects reflect primarily delayed development. The 2006 study by Carney et al. confirms the lack of teratogenicity of PCE, and the developmental effects reported at the lowest concentrations were relatively minor. The LOAEL for maternal effects was 600 ppm and for developmental effects was 250 ppm. The NOAEL for maternal effects was 250 ppm and for developmental effects was 65 ppm.

Growth and Development

Concerns about the neurotoxicity of PCE prompted investigations of the potential effects of exposure during development (Nelson et al. 1980; Manson et al. 1982; Fredriksson et al. 1993; Chen et al. 2002). Nelson et al. (1980) evaluated the effects of inhalation exposure to PCE at 900 ppm 7 h/day on gestation days 7-13 or 14-20. Dams gained less weight and had lower food consumption than controls

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during exposure. Animals were allowed to litter, and pups showed signs of neurobehavioral impairment on certain days of testing. Pups exposed on gestation days 14-20 initially performed more poorly than controls but later were superior on other tests. Significant reductions in acetylcholine were seen in both exposure groups, and reductions in dopamine were seen in the group exposed on gestation days 7-13. Another group of rats exposed to PCE at 100 ppm showed no differences from controls in any of the behavioral tests. Manson et al. (1982) did a followup study on the animals from the Tepe et al. (1982) study to evaluate the potential for postnatal body-weight and skeletal or soft-tissue variants, carcinogenicity, and neurotoxicity. No effects on any of those characteristics were observed. Fredriksson et al. (1993) studied mice exposed orally to PCE (5 or 320 mg/kg per day) on postnatal days 10-16. Mice tested at on postnatal day 17 were unaffected; but at the age of 60 days, changes in all three spontaneous-activity variables (motor activity, rearing, and total activity) and an attenuation of habituation were seen at both doses of PCE. Chen et al. (2002) exposed young rats beginning at weaning (body weight, 45-50 g) to PCE orally at 5 or 50 mg/kg per day 5 days/week for 8 weeks. Effects on pain threshold, locomotor activity, reduction in body-weight gain, and seizure susceptibility were seen at both doses.

The behavioral effects reported in rats (Nelson et al. 1980; Chen et al. 2002) and mice (Fredriksson et al. 1993) exposed to PCE prenatally or postnatally suggest that there may be sensitive windows for neurobehavioral impairment during development. Further study comparing the neurobehavioral, neurochemical, and neuroanatomic changes that follow developmental exposure to PCE are needed. (See the following section.)

Neurologic Effects

Neurotoxicity and Neurobehavioral Effects

Reviews by ATSDR (1997c), the California Environmental Protection Agency (CalEPA 2001), and EPA (2003, 2004) were consulted for this review. Data on accidental and controlled human inhalation and oral exposures and on experimental animal exposures are available.

Acute inhalation and oral exposure of humans has been shown to induce symptoms of CNS depression (dizziness and drowsiness) (ATSDR 1997c). Electroencephalograpic (EEG) changes have been shown after acute inhalation exposure (Hake and Stewart 1977) and after subchronic inhalation exposure (5 days/week for 1 month; Stewart et al.1981) to PCE at 100 ppm. Neurobehavioral changes—such as changes in flash-evoked visual potentials, deficits in vigilance, and deficits in eye-hand coordination—were seen in volunteers exposed to PCE at 50 ppm 4 h/day for 4 days (Altmann et al. 1990, 1992). Oral exposure to doses of PCE ranging from 2.8 to 4 mL (about 4.2 to 6 g) given orally as an anthelminthic resulted in narcotic effects and such associated changes as inebriation, perceptual distortion, and exhilaration (ATSDR 1997c).

A number of animal studies have shown effects on neurologic symptoms and biochemical end points in the brain after exposure to PCE. Acute and short-term inhalation exposure of rats, mice, and dogs to high concentrations of PCE (over 1,000 ppm) produced neurologic signs typical of anesthetic effects, such as hyperactivity, ataxia, hypoactivity, and finally loss of consciousness (summarized by ATSDR 1997c). Savolainen et al. (1977) reported effects of PCE on open-field behavior in rats exposed to PCE at 200 ppm 6 h/day for 4 days. Activity was increased at 1 h but not 17 h after the last exposure, and reduced RNA content and increased cholinesterase were measured in the brain. Mattsson et al. (1998) showed effects of PCE on flash-evoked potentials, somatosensory evoked potentials, and EEG results after acute exposure of rats to PCE at 800 ppm 6 h/day for 4 days when the animals were tested after exposure on the fourth day. Exposure of male Swiss mice to PCE at 596, 649, 684, or 820 ppm for 4 h reduced the duration of immobility experienced by mice when immersed in water (De Ceaurriz et al. 1983); the LOAEL was 649 ppm, and the NOAEL was 596 ppm. Albee et al. (1991) reported EEG changes and decreased latency of flash-evoked potentials and somatosensory evoked potentials in male rats exposed to PCE at 800 ppm 4 h/day for 4 days.

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The effects of intermediate and subchronic inhalation exposure to PCE have also been investigated in several animal studies. Mattsson et al. (1998) found effects on flash-evoked potentials after 13 weeks of exposure of F344 rats to PCE at 800 ppm; the NOAEL was 200 ppm. Male Sprague-Dawley rats exposed continuously to PCE at 600 ppm for 4 or 12 weeks were reported to have reduced brain-weight gain, decreased regional brain weight, and decreased DNA in the frontal cortex and brainstem (Wang et al. 1993). Specific glial proteins (S100 and glial fibrillary acidic protein) and neuronal cytoskeletal proteins (neurofilament 68-kD polypeptide) were also decreased; exposure to 300 ppm had no effect (and 300 ppm was the NOAEL). The authors concluded that the frontal cerebral cortex is more sensitive to PCE exposure than other parts of the brain and that cytoskeletal elements are more sensitive than cytosolic proteins. Rosengren et al. (1986a) exposed male and female Mongolian gerbils to PCE at 60 or 300 ppm for 3 months followed by 4 months without exposure. Changes in S100 (astroglial protein) and reduction in DNA concentrations in various brain regions were observed at 300 ppm, and reduction in DNA in the frontal cortex was seen at 60 ppm. Those effects were replicated by Karlsson et al. (1987). Kyrklund et al. (1988, 1990) reported changes in brain cholesterol, lipids, and polyunsaturated fatty acids in rats after exposure to PCE at 320 ppm for 30 or 90 days. Honma et al. (1980a,b) reported a decrease in acetylcholine in the striatum and an increase in glutamine, threonine, and serine. Kjellstrand et al. (1984) reported increased plasma butyrylcholinesterase concentrations and reduced body weight in white male and female MRI mice exposed to PCE at 37 ppm or greater for 30 days. Hepatic weight was increased at all concentrations (9, 37, 75, and 150 ppm) and continued to be increased 150 days after exposure; changes in hepatic structure were detected during exposure but were reversible. Cessation of exposure reversed the increase in butyrylcholinesterase concentrations. In experiments with various exposure durations, increases in butyrylcholinesterase and hepatic weight were seen after exposure at a time-weighted average of 150 ppm for 30 days.

Three studies have investigated the inhalation exposure of rodents to PCE during development (see also the section "Developmental Effects" above). Nelson et al. (1980) exposed pregnant rats to PCE at 100 or 900 ppm on gestation days 7-13 or 14-20. No effects were seen at 100 ppm, but pup weight gain was decreased in weeks 3-5 after exposure at 900 ppm. Developmental delays of offspring were seen in the exposed groups, and offspring exposed earlier in development had changes in an ascent test and a rotorod test with some increase in motor activity. Significant reductions in acetylcholine were found in assays of the whole brain (minus the cerebellum) after both exposure periods, and there were reductions in dopamine after exposure on gestation days 7-13. The authors concluded that animals exposed late in pregnancy had more behavioral changes than those exposed earlier. Manson et al. (1982), following up on the Tepe et al. (1982) study, found no postnatal effects of exposure to PCE at 1,000 ppm before mating and during pregnancy or only during pregnancy. Pregnant guinea pigs exposed to PCE continuously at 160 ppm on gestation days 33-65 had slightly altered brain fatty acid composition (Kyrklund and Haglid 1991), but the group sizes were very small (four litters each), and the statistical analyses treated each pup as an independent unit.

Year long exposures of Mongolian gerbils to PCE at 120 ppm altered phospholipid content in cerebral cortex and hippocampus (Kyrklund et al. 1984) and caused reductions in cerebellar and hippocampal taurine and increases in hippocampal glutamine (Briving et al. 1986a). However, there was no examination of nervous system structure in those studies to allow correlation of biochemical and behavioral changes. No structural CNS changes were reported in rats and mice exposed to PCE by inhalation at 200 or 400 ppm for 2 years (NTP 1986a).

The effects of oral exposure to PCE have been investigated in only a few studies. Moser et al. (1995) examined adult female F344 rats in a functional observation-screening battery after either a single dose or repeated doses over 14 days. A single dose of PCE at 1,500 mg/kg caused increased lacrimation and gait scores and decreased motor activity; the LOAEL was 150 mg/kg. Effects were greater 4 h after dosing than 24 h after dosing. No effects were seen 24 h after dosing with PCE at 1,500 mg/kg per day for 14 days. EPA (2003) concluded that the difference in effects between single and repeated dosing may reflect behavioral adaptation to PCE exposure. Warren et al. (1996) reported a transient decrease in a 90-min fixed-ratio 40 schedule of reinforcement in male mice exposed to PCE at 480 mg/kg immediately

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before testing; no effect was seen in animals exposed at 160 mg/kg. Blood concentrations correlated with administered dose, but brain concentrations were similar in the two groups. Chen et al. (2002) reported changes in pain threshold, locomotor activity, and seizure susceptibility (after pentylenetetrazol infusion) after exposure to a single dose of PCE at 500 mg/kg in adult rats; at 50 mg/kg, there were changes only in seizure susceptibility.

The effects of PCE exposure on younger animals were reported in two studies. Exposure of young rats (45-50 g) to PCE at 5 or 50 mg/kg per day 5 days/week for 8 weeks resulted in effects on pain threshold, locomotor activity, and seizure susceptibility; changes in locomotion at the high dose; and reduced body-weight gain at 5 and 50 mg/kg (Chen et al. 2002). The review by EPA (2003) raised serious questions about the design and interpretation of the study because of its observational nature and the minor degree of change in latency scores. Fredriksson et al. (1993) exposed 10-day-old MRI mice to PCE orally at 5 or 320 mg/kg per day for 7 days and found increased locomotor activity and total activity at 60 days in both dose groups. Rearing behavior was decreased in the high-dose group. Habituation in response was seen in all three measures, PCE attenuated the response in locomotion and total activity but not rearing. Although EPA (2003) raised issues with the data interpretation in the study and the similarity of the two doses of PCE on locomotion and total activity, the effects on rearing were dose-related. In addition, its criticism of using the pup as the statistical unit ignored to some extent the fact that individual pups were treated in the study.

Two studies that used intraperitoneal exposure have evaluated the neurologic effects of PCE. Umezu et al. (1997) determined that righting reflex was affected after a single intraperitoneal dose of PCE of 4,000 mg/kg but not 2,000 mg/kg in 8-week-old male ICR mice. Ability to balance on a wooden rod was decreased at 2,000 mg/kg but not at 1,000 mg/kg or lower. Response rate on a fixed-ratio 20 schedule was affected at 2,000 mg/kg but not at 1,000 or lower 30 min after treatment. With a fixed-ratio 20 punishment schedule, mice showed an increased response rate at 1,000 mg/kg but not at 500 mg/kg or lower. Motohashi et al. (1993) reported dose-dependent changes in circadian rhythm of 6-week-old male Wistar rats measured at least 1 week after intraperitoneal doses of PCE at 100, 500, or 1,000 mg/kg per day for 3 days. Recovery occurred 3-5 days after exposure ended. Results of studies that use intraperitoneal dosing cannot easily be compared with those of oral or inhalation exposures without pharmacokinetic modeling and development of appropriate conversion metrics.

Cancer

Gliomas were found in two female and four male F344/N rats exposed to PCE at 400 ppm (highest concentration tested) and in one control male (NTP 1986a). The incidence of the tumor was not statistically significant, and one glioma was observed in the control group. Thus, the brain tumors were not considered to have been induced by exposure to PCE.

Immunologic Effects

The effects of PCE on the immune system have been studied less than the effects of TCE. For example, much work has been performed on evaluating the effects of TCE, but not PCE, on autoimmunity. Most immunologic research on PCE has been on allergic sensitization and immunosuppression.

Allergic Sensitization

There is no evidence that PCE can directly induce asthma, but there are suggestive data that it might modulate asthma. Seo et al. (2008) reported that rats given PCE by a single intraperitoneal injection at 0.1 mL/kg showed increased production of regulatory cytokines, including IL-4, and induced histamine release from basophils in animals immunized with a protein allergen. Similar effects were induced by

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PCE in vitro in cells from animals immunized with a protein allergen. Thus, PCE may act as an adjuvant to enhance existing allergic respiratory disease. Epidemiologic studies have indicated that the presence of PCE in the home environment is associated with reduced numbers of IFN-γ containing type 1 T cells (Lehmann et al. 2002). This regulatory cytokine could conceivably skew the normal ratio of type 1 to type 2 T cells to favor the development of asthma in children by allowing a greater proportion of type 2 cells to develop. Earlier studies showed that VOCs may modulate immune cells to favor induction of allergic responses in young children (Lehmann et al. 2001). Further study is needed to clarify whether PCE can induce or modulate allergic diseases.

Immunosuppression

PCE was found to inhibit natural-killer-cell and cytotoxic T-cell activity after in vitro treatment of isolated mouse and rat spleen cells but not in in vivo experiments (Schlichting et al. 1992). In other studies, inhalation of PCE vapors (50 ppm) reduced bactericidal activity against inhaled *Klebsiella pneumoniae* and reduced survival after inhalation challenge with *Streptococcus zooepidemicus* in mice (Aranyi et al. 1986). It was hypothesized that those effects occurred because PCE inhibited alveolar macrophage activity. Such pulmonary host-resistance models can be influenced by a number of factors in the lung, including pulmonary macrophage function and inflammation. The available evidence does not allow any definitive conclusions to be drawn about the immunosuppressive potential of PCE.

Hematopoietic Cancer

F344/N rats were exposed to PCE by inhalation at 0, 200, and 400 ppm 6 h/day 5 days/week for 103 weeks (Mennear et al. 1986; NTP 1986a). A statistically significant increase in mononuclear-cell leukemia in both sexes was shown at both test concentrations, but no apparent dose-response relationship was observed. The NTP concluded that there was clear evidence of carcinogenicity of PCE in male F344/N rats and some evidence in female F344/N rats.

Mononuclear-cell leukemia is a common spontaneous disease of aging F344 rats with incidences in NTP historical control males and females reported to be 50.5% and 28.1%, respectively (Haseman et al. 1998). The condition can exceed 70% in F344 controls (Caldwell 1999; Ishmael and Dugard 2006). Mononuclear-cell leukemia exhibited by F344 rats apparently arises from large granular lymphocytes; that leukemic origin is very uncommon in humans (Caldwell 1999). Given the high background incidence of mononuclear-cell leukemia and other tumors in F344 rats, a series of workshops convened by the NTP considered possible alteratives to the F344 rat as a model for use in bioassays (King-Herbert and Thayer 2006). More recently, a posting on the NTP Web site stated that the outbred Wistar Han rat will be used in standard bioassays rather than the F344 rat because of its attractive characteristics, including an overall low incidence of spontaneous background tumors (NTP 2007). The incidence of mononuclear-cell leukemia in the NTP (1986a) study showed moderate but not clearly PCE-dose-related increases. Considering those factors, induction of mononuclear-cell leukemia in F344 rats exposed to PCE is unlikely to be relevant to prediction of human leukemia risk.

SUMMARY

The purposes of this section are to summarize information from key studies of the more important health effects of TCE and PCE and to describe the scientific evidence of an association between adverse effects in humans and various exposure conditions. TCE and PCE, in contrast with most other chemicals of environmental-health interest, have been extensively studied from a health standpoint. Nonetheless, there remain potential health effects of exposure to TCE and PCE on which there are inconclusive data or no data at all. The committee used a number of criteria in assessing the evidence in human case reports

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and from clinical studies and from controlled investigations with laboratory animals. Criteria used in reaching professional judgments included quality and reliability of key supporting studies, consistency of findings of similar studies, biologic plausibility, toxicologic significance, dose dependence and duration dependence, relative bioavailability and effects after different routes of exposure, and human relevance as determined by toxicokinetic and toxicodynamic concordance. Additional criteria have been used by study authors in assessing the implications of animal cancer bioassay results. The significance of those findings increases with increasing prevalence of tumors in multiple species, strains, and sexes; tumors at multiple sites; occurrence with more than one exposure route; progression from preneoplastic to benign to malignant; metastases; dose dependence; and low or nonexistent spontaneous tumor incidence in the test species.

The primary adverse health effects of TCE and PCE and the conditions under which they were observed are presented graphically below. Figures were prepared for inhalation of TCE (Figure 4-1) and PCE (Figure 4-2) and for ingestion of TCE (Figure 4-3) and PCE (Figure 4-4). The figures are intended to give an overall view of the lowest exposures at which chemically induced anomalies of target organs were reported in reputable studies. Exposure concentrations high enough to also produce anesthesia or narcosis or nonspecific signs of general toxicity (such as malaise, reduced food consumption or reduced body-weight gain, or decreased survival) are indicated. Later in this chapter, LOAELs for selected end points are compared with estimated ranges of TCE and PCE doses by simultaneous ingestion and inhalation experienced by former residents of Camp Lejeune from exposure to contaminated water supplies.

Trichloroethylene

Hepatic Effects

Toxicity

TCE, even in very high oral doses, has little ability to damage the livers of rodents or humans. A typical LOAEL in mice is 500 mg/kg. That dose, when given five times a week for 6 weeks, resulted in a modest increase in release of cytoplasmic enzymes from some damaged hepatocytes. Mice receiving TCE at 100 mg/kg per day on this regimen exhibited only a reversible increase in hepatic weight.

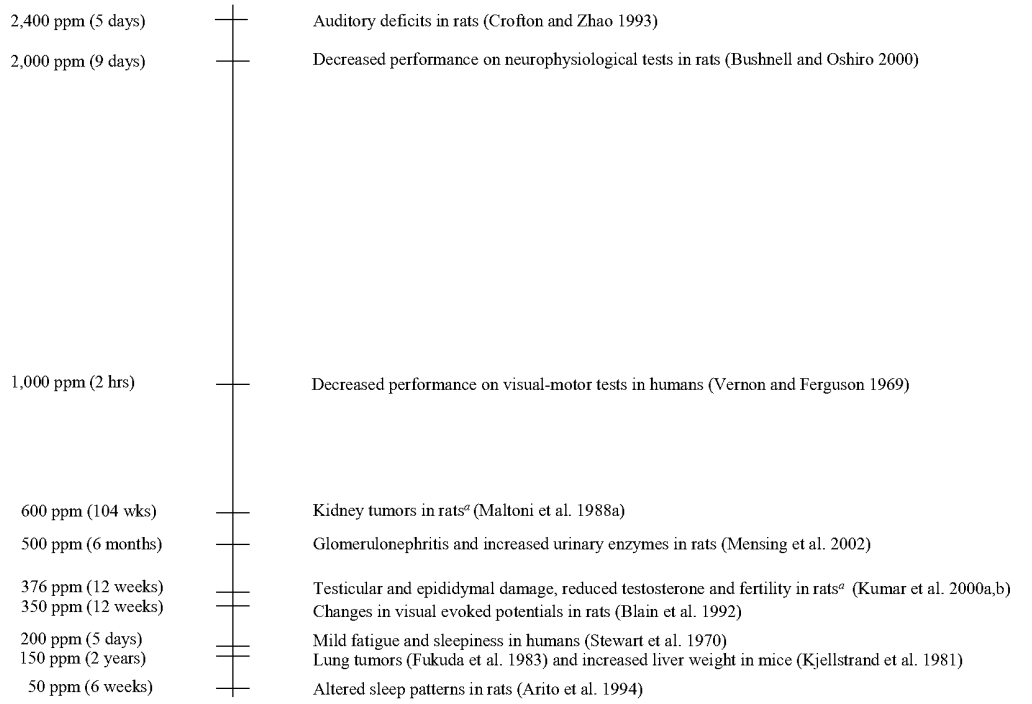
The latter effect is not considered to be toxicologically significant. It should be recognized that TCE (and the other VOCs) at Camp Lejeune must undergo metabolic activation to exert cytotoxicity or mutagenicity and that mice metabolize substantially more TCE than rats and rats more TCE than humans. Reports of hepatotoxicity in patients anesthetized with TCE are rare in the medical literature. No evidence of hepatic injury was manifested in a man rendered unconscious for 5 days by ingesting about 1,370 mg/kg in a suicide attempt.

Cancer

The ability of TCE to cause cancer of the liver and other organs has been the subject of a number of lifetime oral-exposure and inhalation-exposure studies in mice and rats. Daily administration of high doses by both exposure routes resulted in an increased incidence of hepatocellular carcinoma in one strain of one species, the $B6C3F_1$ mouse. It is unlikely that that tumor response is relevant to humans, because mice metabolically activate a much larger fraction of doses of TCE than do humans, the incidence of spontaneous hepatic tumors in male $B6C3F_1$ mice is greater than 42%, and peroxisome proliferation, believed to be a major mechanism by which key TCE metabolites induce hepatic tumors, is negligible in humans. However, some have questioned whether PPARα action is the only relevant mode of hepatic carcinogenesis of such chemicals.

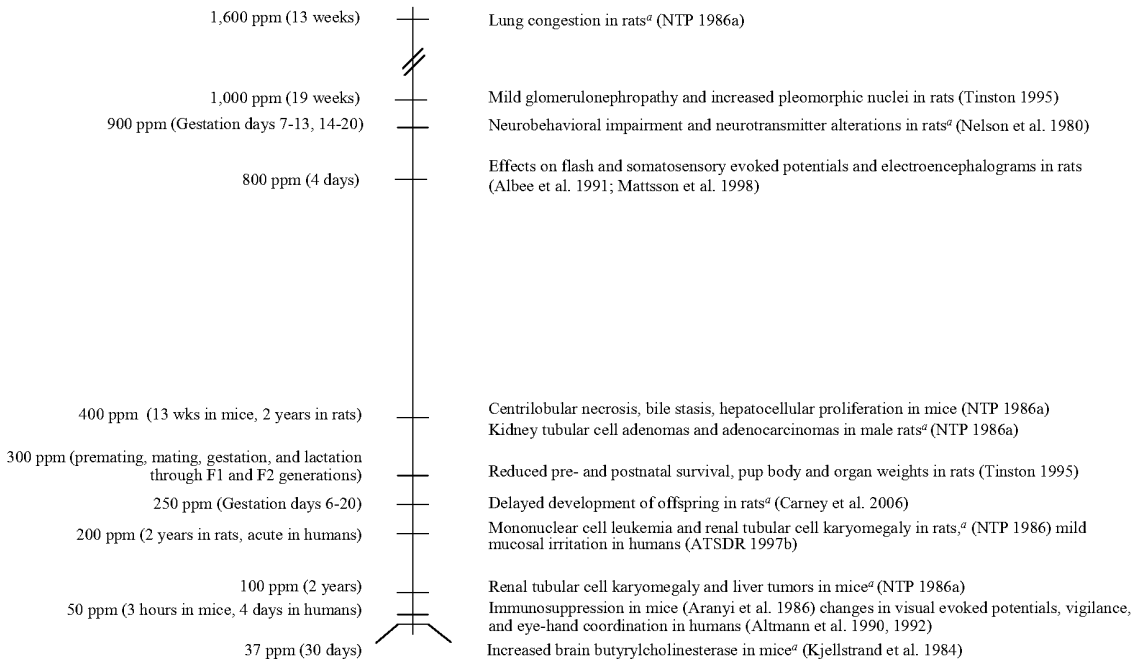
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[a]General toxicity—for example, reduced body weight, weight gain, or food consumption—that may influence effects were observed in the study.

FIGURE 4-1 Effects of exposure to TCE by inhalation. Duration of exposure should be considered in comparing end points that occur after different exposures.



[a]General toxicity—for example, reduced body weight, weight gain, or food consumption—that may influence effects were observed in the study.

FIGURE 4-2 Effects of exposure to PCE by inhalation. Duration of exposure should be considered in comparing end points that occur after different exposures.

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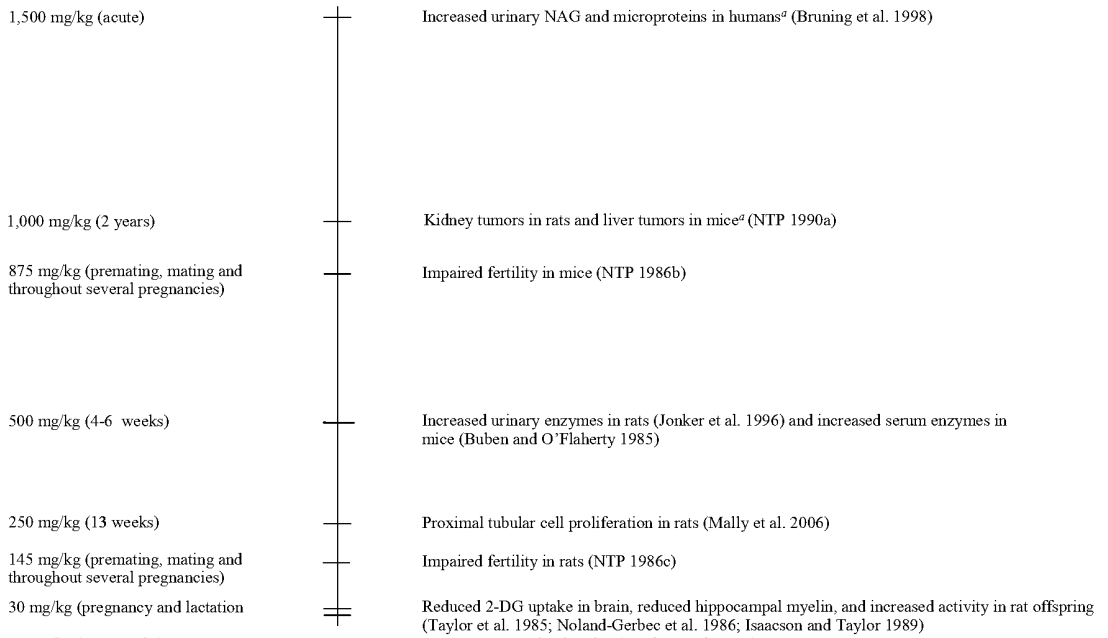


FIGURE 4-3 Effects of exposure to TCE by ingestion. Duration of exposure should be considered in comparing end points that occur after different exposures.

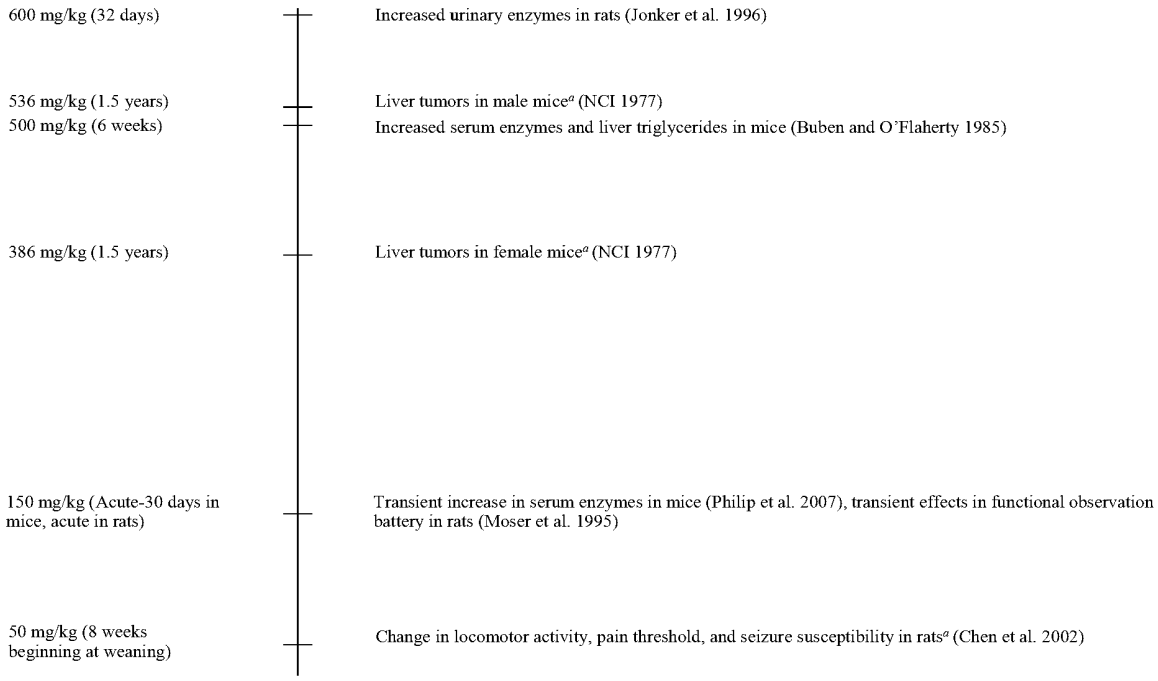


FIGURE 4-4 Effects of exposure to PCE by ingestion. Duration of exposure should be considered in comparing end points that occur after different exposures.

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Renal Effects

Toxicity

TCE has little ability to cause renal damage in rodents subjected to high oral or inhalation exposures for extended periods. A LOAEL of 500 mg/kg was found for mild renal injury in rats gavaged daily for 1 month. LOAELs of 250 and 500 mg/kg for proximal tubular-cell proliferation and karyomegaly, respectively, have been reported. Those responses were observed in male rats exposed orally five times a week for 13 weeks. Nephrosis occurs more commonly and is more serious in rats than in mice in lifetime cancer bioassays. The damage is apparently caused by reactive metabolites of the glutathione conjugation pathway. That pathway is similar qualitatively, but not quantitatively, in rats and humans (rats metabolically activate about 10 times as much). Some workers exposed chronically by inhalation and dermally to TCE sufficient to produce neurologic effects experience renal epithelial toxicity.

Cancer

Chronic exposure to TCE at 1,000 mg/kg per day orally or 600 ppm by inhalation causes saturation of the oxidative metabolic pathway, which leads to increased formation of metabolites via the glutathione pathway. Some of the metabolites are cytotoxic and mutagenic. Male rats, but not female rats and not mice of either sex, exhibit a low incidence of renal-cell carcinoma when subjected to TCE at the aforementioned doses for their lifetimes. Increased rates of renal-cell cancer are also reported in some workers exposed for years to concentrations of TCE high enough to produce CNS effects and renal injury. The recurring cytotoxicity and compensatory cellular proliferation are thought to be prerequisites for renal-cell carcinoma (that is, coupled with the initiating action of mutagenic glutathione metabolites they act as promoters).

Pulmonary Effects

Toxicity

Mice appear to be uniquely sensitive to pulmonary injury by TCE vapor. No reports of lung damage after TCE ingestion were located. Vacuolation of Clara cells was observed in mice that inhaled TCE at concentrations as low as 20 ppm 6 h/day for 5 days. Clara cells are nonciliated bronchiolar mucosal cells that have high CYP2E1 and CYP2F2 activities. The cytochrome P-450s catalyze the oxidation of TCE to chloral and diacetyl chloride, two putative cytotoxic and weakly mutagenic metabolites. Clara cells are numerous and are present throughout mouse airways; they are much less frequent in rats and rare in humans. CYP2E1 activity and TCE metabolism are undetectable in human lung preparations.

Cancer

Chronic TCE exposure has caused increased incidence of lung cancer in three strains of mice but not in rats. Lung tumors have not been seen in mice or rats in five oral TCE bioassays. That may be because presystemic elimination of the orally administered chemical reduced the TCE that reached pulmonary tissues. The TCE-induced mouse lung tumors are not considered relevant to humans since mouse lung tumors are associated with Clara cells containing high CYP2E1 metabolizing activity and human lung contains few Clara cells and undetectable CYP2E1 activity.

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Fertility, Reproductive, and Developmental Effects

Effects of TCE on fertility and reproduction have been seen in several investigations in rodents. In most cases, there were signs of general toxicity (such as body-weight and organ-weight changes and CNS depression) at the same exposure concentrations. Male rats exposed to TCE at 376 ppm 4 h/day 5 days/week for 12 or 24 weeks exhibited reduced body-weight gain, spermatoxicity, and reduced fecundity. CYP2E1, chloral formation, and dichloroacetyl adducts were found in testicular Leydig cells and epididymides of rats and were indicative of production of cytotoxic oxidative metabolites of TCE in the cells that were damaged. CYP2E1 has been found in human epididymal epithelium and Leydig cells. Some TCE oxidative metabolites have been identified in seminal fluid of TCE-exposed mechanics, although the relative metabolic capacities of human and rodent tissues have not been established. DuTeaux et al. (2004a,b) reported a dose-dependent reduction in the ability of sperm from TCE-treated rats to penetrate ova from untreated females in vitro. The male rats ingested TCE at estimated doses of 1.6-3.7 mg/kg per day in drinking water for 14 days. Replication of those findings and further studies of the toxicologic and human significance of that sperm effect are warranted.

Pregnancy outcomes were generally not affected by exposure to TCE at concentrations high enough to be maternally toxic, and there was no evidence of second-generation effects. Previously, there had been reports of cardiovascular defects in offspring of rodents exposed to TCE during gestation. More recently, well-conducted definitive experiments and a robust database have ruled out such developmental anomalies. The possibility of developmental neurotoxicity and immunotoxicity was raised in several publications. Further research is needed to determine whether those results can be duplicated and, if so, to expand the scope of investigation and assess the human relevance.

Cancer

Leydig cell adenoma has been found in male rats in a 2-year oral and a 2-year inhalation cancer bioassay of TCE. It is the most frequently encountered testicular tumor in mice and rats. The spontaneous incidence in old F344 rats is as high as 90%. Most human testicular cancers originate in germ cells or Sertoli cells and occur in young or middle-aged men. Leydig cell adenoma is rare in men, so spontaneous or TCE-induced Leydig cell adenoma is of questionable relevance to humans.

Neurologic Effects

TCE, like many other lipophilic VOCs, inhibits CNS functions as long as it is present at a sufficient concentration in neuronal membranes. Acute effects in humans are usually reversible and range from fatigue and dizziness to intoxication and anesthesia. A number of studies of human subjects have concurred that the inhalation LOAEL for impairment of motor or cognitive functions is 100-200 ppm for several hours. Residual neurotoxic effects (such as trigeminal and olfactory nerve impairment) have been reported in some workers exposed for years to vapor at concentrations that were probably in that range. Auditory deficits, reduced performance of tasks, and other effects were observed in more highly exposed rats, but tolerance usually developed over days or weeks of exposure. LOAELs of 350 and 50 ppm have been reported for changes in visual evoked potentials in rabbits and decreased wakefulness in rats, respectively. The toxicologic significance of those responses in rodents that inhaled TCE several hours a day for weeks has not been established. No definitive oral neurologic studies of TCE were located.

Immunologic Effects

TCE causes allergic sensitization in animal studies, including contact dermatitis and exacerbation of asthma. Some of those effects have been reported in humans after chronic occupational exposure to

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VOCs by inhalation at relatively high concentrations, but further studies are needed to determine whether TCE can induce or modulate allergic diseases in humans. Immunosuppression has also been shown in animal studies after TCE exposure, but it is unclear whether the effects are relevant to humans. Workers exposed to TCE showed increases in IL-2 and IFN-γ and an increase IL-4, but interpretation of these changes is difficult, and the data are too sparse to support definitive conclusions. Toxicologic studies have also shown exacerbation of autoimmune diseases in a genetically modified mouse model (MRL+/+). The relevance of those findings to humans is unclear, although epidemiologic studies have shown a relationship between solvent exposure and scleroderma, glomerulonephritis, and other immune-related diseases (see Chapter 5).

Tetrachloroethylene

Hepatic Effects

Toxicity

PCE, like TCE, has little ability to cause acute, subacute, or chronic hepatotoxicity in rodents or humans. PCE is somewhat more potent because of formation of some additional reactive metabolites. An acute oral LOAEL of 150 mg/kg was reported by Philip et al. (2007), but the serum concentration of a liver-specific enzyme in mice progressively declined as the mice were treated over 30 consecutive days. A NOAEL of 1,440 mg/kg per day was reported in rats that consumed PCE in drinking water for 90 days (Hayes et al. 1986). As described in Chapter 3, ingestion of a chemical in divided doses over several hours reduces its potency. In addition, rats are less susceptible than mice because of their lower capacity for activating PCE metabolically. Humans have even lower capacity than rats.

Cancer

There is clear evidence that near-lifetime inhalation or ingestion of PCE, like that of TCE, results in increased incidence of liver cancer in $B6C3F_1$ mice. Similarly exposed rats do not develop hepatic tumors. PCE's LOAEL is 386 mg/kg for 78 weeks compared with TCE's LOAEL of 1,000 mg/kg for 103 weeks. Trichloroacetic acid, a major metabolite of both PCE and TCE, produces peroxisome proliferation in mouse liver but not rat or human liver. The very high spontaneous hepatic-tumor incidence in $B6C3F_1$ mice and formation of substantially greater quantities of reactive metabolites suggest that mouse hepatic tumors may be of little relevance to humans.

Renal Effects

Toxicity

PCE is somewhat more toxic to the kidneys than TCE. A LOAEL of PCE of 600 mg/kg per day for renal damage was found in rats gavaged for 32 consecutive days. In contrast, consumption of PCE at up to 1,400 mg/kg per day in drinking water for 90 days failed to damage rats' kidneys. That discrepancy can be attributed largely to the kidneys' receipt of lower tissue doses when exposure was in drinking water. A NOAEL of 400 ppm and a LOAEL of 1,000 ppm are described for nephrotoxicity in rats that inhaled PCE several hours a day for a month or more. Karyomegaly was seen in the renal tubular cells of mice and rats that inhaled PCE chronically at as low as 100 and 200 ppm, respectively; the nuclear enlargement may be a predecessor of neoplasia, but a definite link has not been established. Renal effects of PCE are due primarily to metabolites formed via the glutathione conjugation pathway. Equivalent inha-

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lation exposures of rats and humans to PCE at 160 ppm for 6 h showed that biotransformation by the glutathione metabolic pathway was 10 times greater in the rats (Volkel et al. 1998).

Cancer

Chronic inhalation of PCE at 200 or 400 ppm produced renal tubular-cell karyomegaly, hyperplasia and a low incidence of tubular-cell adenoma and carcinoma in male rats. Renal tumors did not occur in female rats or in mice of either sex, although these animals did exhibit karyomegaly.

Pulmonary Effects

Toxicity

There is little evidence of lung injury by inhaled PCE in laboratory animals or humans. Inhalation experiments with human subjects indicate a NOAEL of 150 ppm and a LOAEL of 200-300 ppm for mild irritation of nasal passages. Pulmonary-function measurements do not reveal decrements at those concentrations. Intermittent inhalation of PCE at 1,600 ppm for 13 weeks produced pulmonary congestion in rats; 800 pm did not. There is one report (Aoki et al. 1994) of epithelial degeneration in mice that inhaled PCE at 300 ppm 6 h/day for 5 days. The change was more severe in the olfactory than in the respiratory mucosa.

Cancer

No increases in proliferative lesions or neoplasms of the respiratory tract have been seen in a chronic oral or inhalation cancer bioassay in mice and rats. Although CYP2E1 is abundant in mouse lung, that cytochrome P-450 isozyme is not active as a catalyst of PCE metabolism in the respiratory tract of other rodents or humans.

Other Cancers

An increased incidence of mononuclear-cell leukemia was found in male and female F344 rats that inhaled PCE at 200 or 400 ppm for 103 weeks. The increases were not dose-dependent and were within the incidence range of mononuclear-cell leukemia often seen in control F344 rats. The NTP is no longer using the F344 strain in its cancer bioassay program, because of its high rates of spontaneous cancer of several types. Mononuclear-cell leukemia is rare in people. Thus, that form of leukemia in F344 rats has been judged not to be relevant to humans. Animal cancer bioassay outcomes relevant to human leukemia, multiple myeloma, and non-Hodgkin lymphoma have not been reported.

Fertility, Reproductive, and Developmental Effects

Information on potential effects of PCE on fertility and reproduction is limited. Inhalation of PCE for 5 days did not affect sperm morphology in rats but did result in increased incidence of abnormal sperm heads in mice. The NOAEL and LOAEL for that effect were 100 and 500 ppm, respectively. Long-term exposure of male and female rats to PCE vapor for two generations resulted in CNS depression, decreased body weight during lactation, and nephrotoxicity at 1,000 ppm. There were reductions in live births, litter size, survival, and body weight in the F_2 progeny at that vapor concentration. Those adverse effects may be secondary to maternal body-weight loss and toxicity. More data are needed to clarify the effects of PCE on reproductive function.

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A number of oral and inhalation studies of potential developmental effects of PCE have been conducted in rodents. Experimental protocols have included inhalation of PCE at 300-1,000 ppm before, during, or after pregnancy. Manifestations of developmental delay (such as reduced ossification of vertebrae and soft-tissue dysplasias) have been reported in pups at the relatively high concentration. Ingestion of PCE at 900 mg/kg per day on days 6-19 of gestation, for example, resulted in increased resorptions, reduced weight, and microphthalmia or anophthalmia in rat pups. That daily dose was so high that maternal ataxia and weight loss occurred. Developmental effects at lower concentrations were relatively minor and were not indicative of teratogenicity.

Neurotoxicity

Neurologic Effects

Ingestion and inhalation of sufficient doses of PCE produce CNS depression in rodents and humans. Because PCE is more lipophilic than TCE, it is moderately more potent as a CNS depressant. Deficits in neurophysiologic functions have been reported in volunteers exposed to PCE at as low as 50 ppm for 4 h/day for 4 days (Altmann et al. 1990, 1992). A number of animal studies have revealed neurobehavioral and neurochemical changes in the brains of animals that inhaled PCE at several hundred parts per million for various periods. Mattsson et al. (1998), for example, found altered flash-evoked potentials in rats after 13 weeks of exposure at 800 ppm, but not at 200 ppm. Wang et al. (1993) measured decreases in regional brain weight, DNA content, and glial proteins in rats exposed continuously to PCE at 600 ppm for 4 or 12 weeks. Few researchers, however, have evaluated PCE-induced neurobehavioral and neurochemical changes in the same animals, so interpretation of many of the data is difficult.

Neurodevelopmental Effects

Concerns about possible neurodevelopmental effects in children exposed to PCE prompted several investigations in animals. Chen et al. (2002), for example, described changes in locomotor activity, pain threshold, and pentylenetetrazol-induced seizure thresholds in young rats dosed orally with PCE at 50 mg/kg per day for 8 weeks. Exposure of pregnant rats to PCE at 900 ppm resulted in pups with diminished brain acetylcholine and dopamine concentrations and with neurobehavioral changes on certain days of testing; inhalation of PCE at 100 ppm was without effect. Such reports suggest that there may be periods of neurologic development during which sufficiently high PCE exposures are detrimental. Additional research is needed to determine whether gestational, neonatal, or childhood exposure to such solvents can impair CNS development and function.

Immunologic Effects

Little information is available on the potential of PCE to suppress the immune system or to induce autoimmune diseases. In one study, PCE was found to suppress natural-killer-cell and T-cell activity in vitro but to have no effect on rats in vivo. In a second study, inhalation of PCE at 50 ppm reduced bactericidal activity in mice subjected to inhaled microorganisms. Further investigations of PCE are warranted in light of the apparent effects of TCE on the immune system.

HAZARD EVALUATION OF TRICHLOROETHYLENE AND PERCHLOROETHYLENE EXPOSURE FOR SELECTED END POINTS

The committee used several approaches to consider the health significance of the solvents found in the water supply at Camp Lejeune. Hazard can be defined as the intrinsic characteristic toxicity of a

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chemical compound. The hazard evaluation provides information on the inherent toxic potential of an exposure and is not meant to provide a quantitative estimate of risk. This approach compares the lowest doses of TCE and PCE at which adverse effects were observed in laboratory animals (the LOAELs) with a range of estimated doses from the Camp Lejeune water supply. It is one line of evidence in assessing possible relationships between exposure to TCE and PCE in water at Camp Lejeune and potential health effects.

The lowest dose at which an adverse health effect was observed, the LOAEL, may be subject to some uncertainty, depending on a number of factors, including the doses that were studied, the end point chosen, and the method used to assess the end point; for example, death as an observed LOAEL end point is more certain than a subtle change in an end point that is reversible and of unknown biologic significance. LOAELs from animal studies, on average, are associated with a 10% increase in response rate and can be associated with various risk levels because the statistical power of the studies does not allow observation of lower levels of exposure. Thus, LOAELs do not define a level below which no adverse effects can occur. Nevertheless, determination of a LOAEL generally provides a useful measure of toxic potency. NOAELs are hampered by more uncertainty. A NOAEL is the highest experimental dose at which an adverse effect did not occur. An experimentally determined NOAEL may be substantially lower than the actual NOAEL if the doses administered were too low. The present hazard evaluation was based on LOAELs for selected toxicity end points as described below.

The toxicologic databases on TCE and PCE are extensive, but some data gaps remain for a few end points. LOAELs observed in animal studies selected for this dose comparison represent a range of adverse effects and oral doses. The particular end points were chosen in part because it was assumed that they may be relevant to humans. For TCE, renal tumors in rats were chosen for a chronic high-dose end point (LOAEL, 1,000 mg/kg per day for lifetime oral exposure [NTP 1990a]), renal toxicity in rats was chosen for the medium dosage range (LOAEL, 250 mg/kg per day for 13 weeks [Mally et al. 2006]), and immunosuppression in a sensitive strain of mice was chosen at the lower end of the dosage spectrum (LOAEL, 22 mg/kg per day in drinking water for 4 or 6 months [Sanders et al. 1982]) (see Figure 4-3 and Table 4-3). For PCE: renal toxicity in rats (600 mg/kg per day for 32 days [Jonker et al. 1996]) was selected at the upper end of a series of LOAELs, and neurologic changes in young rats (50 mg/kg per day for 8 weeks [Chen et al. 2002]) at the lower end of LOAEL doses (see Figure 4-4 and Table 4-4).

Uncertainty is associated with the TCE and PCE water concentrations used in the hazard evaluation because they are based on the relatively few mixed water samples analyzed (see Chapter 2). Only a small set of water-quality measurements are available, and those were taken during the 5 years before the contaminated wells were closed, so it is unknown how well they represented the conditions during the preceding decades. In addition, concurrent exposures to organic solvents may have occurred at Camp Lejeune. Studies of mechanisms of VOC interactions (see Chapter 3) indicate that such concurrent exposure is not likely to result in greater than an additive effect. Relatively low doses of multiple VOCs are unlikely to affect the magnitude of adverse health effects appreciably. Additivity is not formally incorporated into this appraisal.

The exercise below is not a health risk assessment. Several assumptions (described below) were used to derive the comparisons, so there is uncertainty and variability in the values. The intent is to provide general comparisons of the lowest doses at which specific adverse health effects were observed in experimental toxicologic studies with a range of estimated contaminant concentrations that may have occurred in the Camp Lejeune water supply.

The following describes the assumptions in the evaluation and illustrative calculations. To provide a standardized basis for comparison, the lowest doses at which a specific adverse effect was seen in toxicologic studies and the exposure estimates are both expressed in standard terms of milligrams of chemical per kilogram of body weight per day (mg/kg per day). Standard assumptions commonly used for hazard evaluations are that adults weigh an average of 70 kg and drink an average of 2 L of water per day and that children weigh an average of 10 kg and drink 1 L of water per day. Exposure via inhalation and dermal absorption of VOCs from water during showering, bathing, dishwashing, and other household ac-

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TABLE 4-3 LOAELs from Animal Studies Used for Comparison with Estimated Daily Human Doses to TCE Related to Water-Supply Measured Concentrations

Range of Doses	End Point	LOAEL, mg/kg per day
High	Kidney cancer, rats	1,000
Medium	Kidney toxicity, rats	250
Low	Immunosuppression, mice (sensitive strain)	22

TABLE 4-4 From Animal Studies Used for Comparison with Estimated Daily Human Doses to PCE Related to Water-Supply Measured Concentrations

Range of Doses	End Point	LOAEL, mg/kg per day
High	Kidney toxicity, rats	600
Low	Neurotoxicity, rats	50

tivities has been shown experimentally to account for as much exposure as that from drinking water that contains the chemicals (see Chapter 3). Therefore, to account for potential inhalation and dermal uptake in addition to ingestion in drinking water, an intake of 4 L/day is assumed for adults and 2 L/day for children. This calculation, therefore, takes into account all three routes of exposure—ingestion, inhalation, and dermal—of both adults and children. Considerable toxicologic data on VOCs are available from inhalation studies. The range of adverse effects is presented in Figures 4-1 and 4-2, but absorbed doses were usually not determined. Duration of exposure is usually specified in animal studies. A conservative assumption used in this hazard evaluation is that humans receive the stated dose daily, although that is very unlikely inasmuch as data presented in Chapter 2 indicate that daily exposures were highly variable.

It is important to note that the evaluation has not taken into account uncertainties and additional considerations (see Chapter 3) related to potentially sensitive populations (such as fetuses and the elderly), possible human interindividual variability in response related to sex and genetic background, such lifestyle factors as level of exercise , underlying diseases, and VOC interactions. Nevertheless, as discussed in Chapter 3, rodents absorb a greater fraction of inhaled VOCs and metabolically activate a substantially greater proportion of their internal dose and are therefore more susceptible than humans to most adverse effects of TCE and PCE.

Chapter 2 summarizes the water-supply data available from the Tarawa Terrace and Hadnot Point water systems. Among the measurements with reported values, TCE concentration in mixed water samples from the Hadnot Point water supply ranged from 1 to 1,400 µg/L (see Table 2-11). Water samples with detectable PCE from the Tarawa Terrace water supply ranged from 1 to 215 µg/L (Maslia et al. 2007). Given the sparse information regarding the range and magnitude of contaminant concentrations in the Camp Lejeune water supply, values that correspond to half the highest measured value, the highest measured value, and twice the highest measured value were selected for this exercise: TCE at 700, 1,400, and 2,800 µg/L and PCE at 100, 200, and 400 µg/L.

The following calculation was carried out to obtain an estimate of human daily exposure: estimated human daily dose (mg/kg per day) = [mixed water concentration (µg/L) × estimated daily intake (oral, inhalation, and dermal) (L/day)]/[body weight (kg)]. A sample calculation follows. For Hadnot Point, the highest measured concentration of TCE in mixed water was 1,400 µg/L. For an adult human, the daily dose received from water containing TCE at 1,400 µg/L is estimated to be

$$\frac{1{,}400\ \mu g/L \times 4\ L/day}{70\ kg} = 80\ \mu g/kg\ per\ day = 0.08\ mg/kg\ per\ day.$$

Half the highest measured TCE concentration in the water supply (700 µg/L) yields an estimated dose of 0.04 mg/kg per day for adults, and twice the highest measured concentration of TCE (2,800 µg/L) yields

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an estimated dose of 0.2 mg/kg per day for adults. For a child, the daily dose received from water containing TCE at 1,400 µg/L is estimated to be

$$\frac{1{,}400\ \mu g/L \times 2\ L/day}{10\ kg} = 280\ \mu g/kg\ per\ day = 0.3\ mg/kg\ per\ day.$$

Half the highest measured TCE concentration in the water supply (700 µg/L) yields an estimated dose of 0.1 mg/kg per day for a child, and twice the highest measured concentration of TCE (2,800 µg/L) yields an estimated dose of 0.6 mg/kg per day for a child.

Table 4-3 shows the LOAELs from animal studies used to compare with the estimated human TCE doses related to a range of possible water-supply exposure concentrations. A comparison of LOAELs for health end points selected from TCE animal studies with the exposure estimates is summarized here:

- *Kidney cancer.* The LOAEL of TCE for lifetime oral exposure leading to kidney cancer in the rat is 1,000 mg/kg per day (NTP 1990a). The estimated human adult dose at Camp Lejeune is 25,000 times lower than the LOAEL for exposure at half the highest water-supply concentration, 12,500 times lower than the LOAEL for exposure at the highest concentration, and 5,000 time lower than the LOAEL for exposure at twice the highest concentration for a lifetime exposure. For a child, the comparable estimates are 10,000, 3,350, and 1,700 time lower than the LOAEL, respectively.
- *Renal toxicity.* The LOAEL of TCE for renal toxicity in the rat dosed orally for 13 weeks is 250 mg/kg per day (Mally et al. 2006). The estimated human adult dose at Camp Lejeune is 6,250 times lower than the LOAEL for exposure at half the highest water-supply concentration, 3,125 times lower than the LOAEL for exposure at the highest concentration, and 1,250 times lower than the LOAEL for exposure at twice the highest concentration. For a child, the comparable estimates are 2,500, 830, and 415 times lower than the LOAEL, respectively.
- *Immunosuppression.* The LOAEL of TCE for immunosuppression in a sensitive strain of mouse ingesting TCE for 4 or 6 months is 22 mg/kg per day (Sanders et al. 1982). The estimated human adult dose at Camp Lejeune is 550 times lower than the LOAEL for exposure at half the highest water-supply concentration, 275 times lower than the LOAEL for exposure at the highest concentration, and 110 times lower than the LOAEL for exposure at twice the highest concentration. For a child, the comparable estimates are 220, 75, and 40 times lower than the LOAEL, respectively. These differences are relatively smaller than for kidney cancer and kidney toxicity. As stated earlier in the chapter, uncertainties exist regarding this end point since there is relatively little toxicologic information on TCE and immune effects. Additional research may be needed on the potential immunosuppressive effects of TCE.

For PCE, the daily dose received from water at the maximum measured concentration (200 µg/L) in the water supply for an adult human is estimated to be

$$\frac{200\ \mu g/L \times 4\ L/day}{70\ kg} = 0.01\ mg/kg\ per\ day.$$

Exposure to half the highest measured water supply concentration (100 µg/L) yields a dose of 0.006 mg/kg per day for an adult human and exposure to twice the highest measured water supply concentration (400 µg/L) yields a dose of 0.02 mg/kg per day. For a child, the daily dose received from water containing PCE at the maximum measured concentration (200 µg/L) is estimated to be

$$\frac{200\ \mu g/L \times 2\ L/day}{10\ kg} = 0.04\ mg/kg\ per\ day.$$

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Exposure to half the highest measured water supply concentration (100 µg/L) yields a dose of 0.02 mg/kg per day for a child and exposure to twice the highest measured water supply concentration (400 µg/L) yields a dose of 0.08 mg/kg per day.

A comparison of LOAELs for each of the two health end points selected from PCE animal studies (Table 4-4) with the estimated doses from the water supply is summarized here:

- *Renal toxicity*. The LOAEL for renal toxicity in the rat dosed orally with PCE for 32 days is 600 mg/kg per day (Jonker et al. 1996). The estimated human adult dose at Camp Lejeune is 100,000 times lower than the LOAEL for exposure at half the highest water-supply concentration, 60,000 times lower than the LOAEL for exposure at the highest concentration, and 30,000 times lower than the LOAEL for exposure at twice the highest concentration. For a child, the estimates are 30,000, 15,000, and 7,500 times lower than the LOAEL, respectively.
- *Neurotoxicity*. The LOAEL of PCE for neurotoxic effects in rats is 50 mg/kg per day for 8 weeks (Chen et al. 2002). The estimated human adult dose at Camp Lejeune is 8,300 times lower than the LOAEL for exposure at half the highest water-supply concentration, 5,000 times lower than the LOAEL for exposure at the highest concentration, and 2,500 times lower than the LOAEL for exposure at twice the highest concentration. For a child, the comparable estimates are 2,500, 1,250, and 625 times lower than the LOAEL, respectively. As noted earlier in this chapter, there is a need for additional research to clarify the neurotoxic effects of PCE.

The comparisons above included health end points observed in animals that were considered relevant to humans. Renal toxicity and cancer, neurotoxicity, and immune-related effects have been reported in some epidemiology studies and in clinical reports. The dose comparisons[1] suggest considerable differences between the estimated doses from human exposure to contaminated water supplies at Camp Lejeune under conservative assumptions of exposure and the lowest doses associated with the development of renal toxicity, kidney cancer, neurotoxicity, and immunosuppression in rodents. The drinking-water doses at Camp Lejeune are substantially lower. As pointed out in this section, however, each and

[1]One member, Lianne Sheppard, objected to inclusion of the hazard evaluation in the report as written and offered the following explanation: "Comparison of toxicology-based LOAEL values with estimated exposures to the Camp Lejeune population uses questionable logic to support inference that adverse health effects are unlikely to have occurred. Although LOAEL estimates give evidence about the presence of a hazard, they should not be used to make inference about the absence of hazard at lower doses. The absence of evidence of a hazard (e.g., at levels below the LOAEL) cannot be equated with evidence of the absence of hazard (Altman and Bland 1995; Fleming 2008). Because of their small sample size, animal studies are only able to identify hazards that induce high levels of response (on average 10% increase in response for the LOAEL). Moreover, levels of excess response considered acceptable in humans are much lower than 1 in 10, typically on the order of 1 in 10,000 to 1 in 1 million (EPA 2005). While low-dose extrapolation involves additional untestable assumptions, dividing the LOAELs by 1,000 to 100,000 provides an alternative approach to the informal hazard evaluation presented above. This second approach compares Camp Lejeune exposures with an acceptable hazard in humans, as extrapolated from toxicologic studies. The results lead to strikingly different conclusions because they yield acceptable hazards that are both larger and smaller than the estimated exposures; indeed, some are several orders of magnitude lower than Camp Lejeune exposures. Alternatively, standard practice would replace informal hazard evaluation with a formal risk assessment, although this task was outside the committee charge. Despite my reservations on this one area of the assessment, I support the overarching findings and recommendations of the report."

Other members disagree with Dr. Sheppard's characterization that the hazard evaluation is based on questionable logic. The reasons for this are stated in the text. The validity of results using the approach she outlines above is questioned by some committee members. There were varying views among committee members on the value of the information generated by the hazard evaluation effort, ranging from members who found it quite useful because it provided a rough benchmark for speculating about the likelihood of adverse health effects, to members who placed less reliance on results, given limited exposure information and their uncertainty about the applicability of toxicologic information. Regardless of the approach taken to the hazard evaluation, however, all committee members strongly support the overarching findings and recommendations of the report.

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every source of uncertainty (e.g., interindividual variability, lifestyle, genetic background, exposure assessment, completeness of the database) has not been factored into this estimate since it is a hazard evaluation procedure and not a health risk assessment.

ALLOWABLE LIMITS OF VOLATILE ORGANIC COMPOUNDS IN DRINKING WATER

Current regulatory standards termed maximum contaminant levels (MCLs) for several VOCs in drinking water, including TCE and PCE, were developed by EPA in the middle 1980s (50 Fed. Reg. 46880 [1985]; 52 Fed. Reg. 25690 [1987]; Cotruvo 1988). Under the U.S. Safe Drinking Water Act, the public-health goal or maximum contaminant level goal (MCLG) for a compound was initially determined. The MCLG is the concentration that would result in "no known or anticipated adverse effect on health" with a large margin of safety. Second, an MCL, or enforceable standard, was set as close as feasible to the MCLG; technical and economic factors were taken into consideration. EPA consulted the International Agency for Research on Cancer guidelines when assessing epidemiologic and animal cancer data and in its own qualitative weight-of-evidence scheme for determining the potential for a compound to increase cancer risk in humans. TCE and PCE fell into category I in the latter scheme, in which the MCLG by definition equals zero as an aspirational goal. Economic considerations for water treatment were also deliberated. Technical feasibility focused on analytic considerations; the lowest concentrations that can be reliably detected within specified limits of precision and accuracy during routine laboratory operations (practical quantitation limits) were determined. With that approach, an MCL of 0.005 mg/L (5 µg/L or 5 ppb) was set for selected VOCs, including TCE and PCE.

In 2005, EPA issued new guidelines for carcinogen risk assessment in which incorporation of increased scientific understanding of the biologic mechanisms that can cause cancer was supported for inclusion in risk assessments with other improved risk-assessment practices (EPA 2005). In the more than 20 years since the original MCLs were established, considerable kinetic and biologic mechanism-of-action information on TCE and PCE has been published, as reviewed in the present report. There are different approaches to risk assessment that yield different results. At least one recent study has explored different approaches, including the use of contemporary published elements of TCE's biologic mode of action and a cancer-risk model that was the best fit to the data (Clewell and Andersen 2004). The latter approach yielded a TCE concentration of 265 µg/L in drinking water; below this concentration, a carcinogenic hazard to human health was deemed unlikely. This is one example of the possible application of toxicologic and mechanistic biologic data to a cancer health risk assessment for TCE, which yields a value greater than one based on analytical limits of detection. EPA is currently updating its risk assessments on TCE and PCE and is considering new data and different assessment approaches as part of its reassessments. In summary, the few TCE and PCE measurements available from mixed drinking-water samples at Camp Lejeune (see Chapter 2) indicated that some samples exceeded the MCLs derived as briefly described above.

CONCLUSIONS

TCE and PCE are well-studied compounds compared with most other compounds of environmental concern. On the basis of the review presented above, the committee concludes that the strongest evidence of health effects of relevance to humans are renal toxicity, kidney cancer, neurobehavioral effects, and immunologic effects, which have generally been observed at high concentrations in a workplace setting and in exposure to tens to thousands of milligrams per kilogram of body weight in animal studies. Discussion of the toxicologic evidence in context with the epidemiologic evidence on TCE and PCE (presented in Chapter 5) is provided in Chapter 7. The evidence on renal toxicity and cancer is particularly convincing because concordance has been found in the bioactivation of TCE and PCE and in their modes of action in rodents and humans. However, gaps in the toxicologic database preclude drawing conclusions about some other health effects related to the nervous system and the immune system, par-

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ticularly with regard to potential effects on the developing or young animal. Implicit inherent limitations of toxicologic studies are that relatively homogeneous populations of laboratory animals are used and exposures are typically to single chemicals. On average, the lowest increase in effect that can usually be detected (LOAEL) is around 10% due to statistical power related to the number of animals that can be tested in any one study. In the instances of TCE and PCE, however, rodents are more susceptible to toxic effects.

A central issue in toxicology (and at Camp Lejeune) is whether doses were sufficient to produce specific adverse effects. The lowest doses at which adverse health effects have been seen in animal or clinical studies are many times higher than the worst-case (highest) assumed exposures at Camp Lejeune. However, that does not rule out the possibility that other, more subtle health effects that have not been well studied could occur, although it somewhat diminishes their likelihood.

Another important issue is whether any adverse effects that may have occurred were reversible or permanent and (still) detectable when an epidemiology study might be conducted. Observations in animal studies indicate that very high acute or chronic doses of TCE or PCE are necessary to injure renal proximal tubular cells. Results of occupational-exposure studies indicate that relatively high, chronic exposures result in modest, reversible changes in the most sensitive indexes of renal injury in workers. Thus, it is unlikely that renal toxicity would be a useful end point to examine in future epidemiology study of Camp Lejeune residents. A similar conclusion can be drawn with regard to the occurrence and detection of hepatic toxicity. Reproductive and developmental effects in rodents were quite modest and often secondary to general toxicity, decreased food intake, and reduced body-weight gain resulting from high maternal doses of TCE and PCE. The toxicologic data provide strong evidence that neither solvent is associated with congenital malformations in rats. Thus, on the basis of this review, reproductive effects and hepatorenal toxicity are probably not of great concern at Camp Lejeune.

There is reasonable interspecies concordance between rats and humans in the bioactivation of TCE and PCE and in their mode of induction of kidney cancer. A low incidence of kidney cancer has been seen in workers exposed for many years to TCE at concentrations high enough to cause dizziness, headache, and other reversible neurologic effects. The background incidence of kidney cancers in unexposed persons is minimal. Nevertheless, there is little likelihood of identifying any increased incidence of renal tumors in the relatively small population that may be available for study at Camp Lejeune.

Irreversible neurobehavioral effects associated with solvent exposure generally are chronic and result from high doses. Solvent abusers and workers chronically exposed to high vapor concentrations may exhibit various neurobehavioral effects and residual brain damage. Fetuses, infants, and young children exposed to such organic solvents as TCE and PCE at lower concentrations may experience subtle neurodevelopmental effects, but no relevant investigations were identified. There are few data from animal studies on this topic.

Immune suppression and autoimmunity related to TCE exposure have been demonstrated in some sensitive animal models. TCE-induced glomerulonephritis and scleroderma occur in low incidences in highly exposed worker populations. Much less is known about the potential immunologic effects of PCE (particularly as related to exposures during development), which may warrant further consideration for inclusion in studies of populations exposed to TCE or PCE.

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5

Review of Epidemiologic Studies

This chapter reviews a large body of epidemiologic literature on specific drinking-water contaminants at Camp Lejeune, focusing primarily on trichloroethylene (TCE) and tetrachloroethylene (perchloroethylene, PCE). Most of the literature involves populations exposed occupationally to those solvents and other industrial chemicals. The goal is to determine whether exposure to TCE or PCE is associated with specific health outcomes. (Appendix D provides brief reviews of the epidemiologic literature on the six additional drinking-water contaminants identified in Chapter 2 as of possible concern—vinyl chloride, 1,1-dichloroethylene, 1,2-dichloroethylene, methylene chloride, benzene, and toluene.) Chapter 6 gives special consideration to studies of other communities whose populations and exposure to contaminants in drinking water are similar to those at Camp Lejeune. Chapter 7 provides an integrated discussion of the epidemiologic evidence in context with the toxicologic evidence on TCE and PCE presented in Chapter 4. Epidemiologic studies of former residents of Camp Lejeune are reviewed separately in Chapter 8.

EVALUATING THE EPIDEMIOLOGIC LITERATURE

To manage the review of the vast literature on the chemicals of concern at Camp Lejeune, the committee decided to use a categorization approached developed by the Institute of Medicine (IOM) for evaluating epidemiologic data on chemicals. The approach involves a comprehensive review of the epidemiologic literature on individual chemicals and assigning one of five categories to the evidence (see Box 5-1 for IOM's categories of association). An assessment of whether the data indicate a *statistical association* between the chemicals and various cancer and noncancer health outcomes is the basis for the categorizations, except for the highest category of sufficient evidence of a causal relationship, which is also based on experimental data and evidence of causality. IOM's approach has been used to evaluate exposure of veterans of the Vietnam War (IOM 1994, 1996, 1999) and the Gulf War (IOM 2003).

Statistical associations are generally estimated by calculating relative risks (RRs) or odds ratios (ORs). In our review, a "statistical association" does not imply that the measure of association is statistically significant or causal, only that an association of potential interest has been reported. The committee reviewed the conclusions of each study in light of its strengths and weaknesses, taking into account the strength of the association (the magnitude of the OR or RR estimate), the influence of exposure-measurement error, selection bias, statistical precision, and confounding bias. The coherence of the epidemiologic evidence was then assessed, and an assignment made to a category of association.

In the sections below, the committee used the conclusions drawn by IOM (2003) on cancer and noncancer health end points of TCE or PCE exposure as a starting point for its evaluation. Literature searches were performed on Medline to identify new (2003-2008) peer-reviewed epidemiologic studies of exposure to TCE, PCE, or mixtures of chlorinated solvents and various health outcomes. The committee weighed the strengths and weaknesses of the new evidence to draw conclusions about whether IOM's

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BOX 5-1 Five Categories Used by IOM to Classify Associations (IOM 2003)

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 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 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 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 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.

categorizations are still valid or should be changed. Each health-outcome section below brief summarizes the evidence as described in the 2003 IOM report, reviews the new evidence, and presents conclusions drawn from the totality of the epidemiologic evidence. Appendix E presents tables of details on each of the new studies. Whenever possible, the committee evaluated the associations between TCE or PCE and the end points and reported findings specifically on those solvents. If a study addressed solvent mixtures, the evidence was examined and a category of association was determined with the default presumption that there was not information specifically on TCE or PCE. The committee expands on IOM's approach in Chapter 7 by explicitly considering how the toxicologic evidence presented in Chapter 4 adds to the weight of evidence in characterizing health risks related to the TCE and PCE.

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STUDIES OF TRICHLOROETHYLENE AND PERCHLOROETHYLENE

Cancer End Points

Oral and Pharyngeal Cancer

IOM 2003 Conclusions

IOM (2003) found little evidence of a consistent association between chronic exposure to PCE and an increased risk of oral or pharyngeal cancer ("oral cancer"). The studies evaluated often involved only a small number of exposed persons. No studies specifically assessed TCE in relation to oral cancer, and no increase in risk was found in connection with solvent mixtures. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and oral cancer.

2008 Evaluation

The updated literature on TCE and oral cancer included five cohort studies with cancer incidence or mortality data (Hansen et al. 2001; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007). Two studies of Danish workers (Hansen et al. 2001; Raaschou-Nielsen et al. 2003) evaluated the risk of oral cancer. Hansen et al. found an increased risk in exposed male workers based on only seven exposed cases. In the larger study by Raaschou-Nielsen et al. (2003), a standard incidence ratio (SIR) of 1.8 (95% confidence interval [CI], 0.84-3.24) was found for women employed at least 3 mo; the SIR for men (95 exposed cases) was only 1.1 (95% CI, 0.90-1.36). Other studies of workers in different industries did not report a consistently increased risk, although most involved only a small number of exposed persons. There was an indication of an increased risk in women potentially exposed to TCE in the Raaschou-Nielsen study, but the totality of the evidence does not indicate a consistent pattern of increased risk in TCE-exposed persons.

The updated literature on PCE and oral cancer included two cohort studies with cancer mortality or incidence data (Blair et al. 2003; Chang et al. 2003, 2005). Neither study reported an increased risk posed by PCE exposure, but they involved only small numbers of exposed persons.

- The updated literature on PCE and TCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and oral cancer.

Nasal Cancer

IOM 2003 Conclusions

IOM (2003) found no studies that specifically evaluated TCE or PCE but reviewed a few studies that examined other solvents and nasal cancer. Increased but imprecise RR estimates were found in a Chinese study of benzene exposure and a study of shoemakers in England and France (Fu et al. 1996; Yin et al. 1996). IOM concluded that the evidence was inadequate/insufficient to determine whether an association exists between chronic exposure to solvents and oral cancer.

2008 Evaluation

No new studies of chronic exposure to solvents and nasal cancer were found.

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- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and nasal cancer.

Laryngeal Cancer

IOM 2003 Conclusions

Two studies (Blair et al. 1990; Vaughan et al. 1997) found an increased but imprecise risk posed by PCE and dry-cleaning solvents. IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to PCE, TCE, or other solvents and laryngeal cancer.

2008 Evaluation

The updated literature on TCE and laryngeal cancer included four cohort studies with cancer incidence or mortality data (Hansen et al. 2001; Chang et al. 2003; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007). One study of Danish workers (Raaschou-Nielsen et al. 2003) found an SIR of 1.7 (95% CI, 0.33-4.82) for women employed at least 3 months (on the basis of three exposed cases); the SIR for men was 1.2 (95% CI, 0.87-1.52) on the basis of 53 exposed cases. Boice et al. (2006) reported a standardized mortality ratio (SMR) of 1.45 (95% CI, 0.18-5.25) on the basis of two exposed cases.

The updated literature on PCE and laryngeal cancer included two cohort studies with cancer mortality data (Blair et al. 2003; Chang et al. 2003). Blair et al. (2003) performed an updated mortality assessment of a cohort of dry cleaners and found an increased risk in workers with medium to high exposure (SMR, 2.7; 95% CI, 1.0-5.8) on the basis of only six exposed cases. Chang et al. (2003) did not find any exposed cases in a Taiwanese cohort of electronics manufacturing workers.

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and laryngeal cancer.

Esophageal Cancer

IOM 2003 Conclusions

IOM (2003) considered evidence from several cohort and case-control studies of esophageal cancer in relation to chronic exposure to solvents, including TCE and PCE. Although several studies had positive results (Blair et al. 1990; Vaughan et al. 1997; Boice et al. 1999; Ruder et al. 2001), IOM was unable to reach a consensus on PCE but concluded that there was inadequate/insufficient evidence to determine whether an association exists between TCE and other solvents and solvent mixtures and esophageal cancer.

2008 Evaluation

The new literature on TCE and esophageal cancer included an update on the Danish worker cohort (Raaschou-Nielsen et al. 2003) and three cohorts studies with cancer incidence or mortality data (Chang et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007). One study of Danish workers (Raaschou-Nielsen et al. 2003) found an SIR of 1.9 for men employed at least 3 months. Other studies did not find a pattern of increased risk.

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The updated literature on PCE and esophageal cancer included two cohort studies with cancer mortality data and one case-control study (Blair et al. 2003; Chang et al. 2003; Lynge et al. 2006). Blair et al. (2003) performed an updated mortality assessment of a cohort of dry cleaners and found an increased risk in workers (SMR, 2.2; 95% CI, 1.5-3.3) on the basis of 26 exposed cases. No exposure-response pattern of increased risk was found when results were examined by exposure group. Chang et al. (2003) did not find any exposed cases in a Taiwanese cohort of electronics manufacturing workers, and Lynge et al. (2006) found a decreased risk.

- The updated literature on TCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the solvent and esophageal cancer.
- On the basis of the results of the Blair et al. (2003) study of dry cleaners and other studies, the committee concludes that there is limited/suggestive evidence of an association between chronic exposure to PCE and esophageal cancer. This constitutes a new conclusion, in that a consensus was not reached in the 2003 IOM report.

Stomach Cancer

IOM 2003 Conclusions

IOM (2003) reviewed five occupational-cohort studies assessing the association between TCE and stomach cancer (Wilcosky et al. 1984; Anttila et al. 1995; Blair et al. 1998; Boice et al. 1999; Hansen et al. 2001). A study of Finnish workers biologically monitored for exposure (on the basis of urinary trichloroacetic acid) showed an increased risk of stomach cancer (SIR, 1.28; 95% CI, 0.75-2.04), and the risk was greater in workers who had their first measurement 20 years before (SIR, 2.98; 95% CI, 1.20-6.13). However, there was no evidence of an exposure-response relationship with urinary trichloroacetic acid concentrations (Anttila et al. 1995). The overall conclusions drawn from the other studies were mixed. Similarly, the results of the three cohort studies of PCE-exposed populations were mixed (SMR, 0.61-1.42) (Blair et al. 1990; Ruder et al. 1994; Boice et al. 1999). Results of three mortality cohort studies (Garabrant et al. 1988; Costantini et al. 1989; Acquavella et al. 1993) and a case-control study (Ekstrom et al. 1999) of workers exposed to unspecified mixtures of organic solvents and a cohort study of Swedish patients with acute solvent-related disorders (Berlin et al. 1995) were predominantly null except for increased risk of stomach cancer in a cohort of shoemakers in England and Florence (Fu et al. 1996). IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to the solvents reviewed and stomach cancer.

2008 Evaluation

The committee identified several new cohort studies of occupational groups exposed to TCE or PCE (Blair et al. 2003; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007). The reported results on stomach cancer were mixed, as were those in the IOM (2003) report. However, in a case-control study of a community living downstream of an electronics factory and potentially exposed to PCE, the mortality odds ratio (MOR) for stomach cancer was increased (2.18; 95% CI, 0.97-4.89) (Lee et al. 2003).

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and stomach cancer.

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Colon Cancer

IOM 2003 Conclusions

IOM (2003) reviewed five cohort studies with incidence or mortality data (Anttila et al. 1995; Blair et al. 1998; Boice et al. 1999; Hansen et al. 2001) and one case-control study (Fredriksson et al. 1989) on the association between TCE exposure and colon cancer. The Blair et al. study showed a positive association between TCE exposure and both mortality and incidence, but there was evidence of an exposure-response relationship only between years of work and incidence (Blair et al. 1998). The results of the other studies were mixed, and IOM was not able to reach a consensus opinion about chronic exposure to TCE and colon cancer. For PCE, IOM included one cohort study of intestinal-cancer mortality in dry cleaners (Ruder et al. 2001) and two case-control studies—one defining exposure on the basis of work as a dry cleaner (Fredriksson et al. 1989) and the other on the basis of exposure to contaminated drinking water on Cape Cod (Paulu et al. 1999). The results showed evidence of increased risk, but there was no evidence of an exposure-response relationship, the numbers were small, and diseases were not well defined. Therefore, IOM concluded that the literature was inadequate/insufficient to determine whether an association exists between PCE exposure and colon cancer. IOM also reviewed three studies of unspecified mixtures of organic solvents (Fredriksson et al. 1989; Anttila et al. 1995; Berlin et al. 1995). Increased risks were observed only in the Fredriksson study, and in all three the numbers of exposed cases were small. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to unspecified solvents and colon cancer.

2008 Evaluation

The updated literature on TCE and colon cancer includes six occupational-cohort studies with incidence or mortality data on colon cancer or colon and rectal cancer. In most studies, the SIRs or SMRs were around 1.1 (Raaschou-Nielson et al. 2003; Boice et al. 2006; Sung et al. 2007). Zhao et al. (2005) assessed incidence and mortality in a cohort of aerospace workers. The SMRs were also around 1.1, but the SIRs were not increased, and there was no evidence of an exposure-response relationship (exposure was defined by an industrial-hygiene review). In a study of test-stand mechanics determined by an industrial-hygiene review to be exposed to TCE, the SMR was 1.66 (95% CI, 0.54-3.87) (Boice et al. 2006). A study of electronics and mechanical workers in Taiwan exposed to TCE and PCE found an SMR of 1.36 (95% CI, 0.82-2.13) on the basis of 19 cases (Chang et al. 2003). In an incidence study of the same population, there was no clear evidence of an association (Chang et al. 2005). Two studies of community exposures to TCE and PCE in drinking water did not find increased risks of colon cancer (Morgan and Cassady 2002; Lee et al. 2003). IOM also reviewed one cohort of dry cleaners exposed to PCE (Blair et al. 2003). The SMR was 1.2 (95% CI, 0.9-1.5) and there was some evidence of an exposure-response relationship. No new studies on exposure to unspecified mixtures of organic solvents and colon cancer were found.

- The committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and colon cancer. The conclusion regarding TCE constitutes a new conclusion, in that a consensus was not reached in the 2003 IOM report.

Rectal Cancer

IOM 2003 Conclusions

IOM (2003) reviewed five cohort studies with incidence or mortality data (Anttila et al. 1995;

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Blair et al. 1998; Morgan et al. 1998; Boice et al. 1999; Hansen et al. 2001) and one case-control study (Dumas et al. 2000) on the association between exposure to TCE and rectal cancer. Although increased risks were observed in all but the Blair et al. study, the numbers of cancers in exposed persons were small, no more than 12 in each study. IOM included two studies in its review of PCE and dry-cleaning solvents: a cohort study of intestinal cancer in dry-cleaning workers (Ruder et al. 2001) and a study of colon and rectal cancer in Cape Cod residents exposed to contaminated water (Paulu et al. 1999). Both studies were discussed above under "Colon Cancer." Three cohort studies assessed the incidence of or mortality from rectal cancer and exposure to unspecified mixtures of organic solvents (Garabrant et al. 1988; Anttila et al. 1995; Berlin et al. 1995). Excess risks were observed only in the Anttila et al. study. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or solvent mixtures and rectal cancer.

2008 Evaluation

The updated literature on TCE and rectal cancer included two cohort studies. Raaschau-Nielsen et al. (2003) observed SIRs of 1.1 in men and women working in jobs involving TCE exposure. Chang et al. (2003) assessed mortality in a cohort of electronics manufacturers exposed to TCE and PCE. On the basis of only 15 exposed cases (13 in women and two in men), the SMR for women was increased (1.67; 95% CI, 0.89-2.85), but the SMR for men was not (0.73; 95% CI, 0.08-2.65). An additional cohort study reported an increased risk of rectal-cancer mortality in dry cleaners (SMR, 1.3; 95% CI, 0.7-2.2) (Blair et al. 2003).

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and rectal cancer.

Pancreatic Cancer

IOM 2003 Conclusions

IOM (2003) reviewed five occupational-cohort studies with incidence or mortality data on the association between TCE exposure and pancreatic cancer (Anttila et al. 1995; Blair et al. 1998; Morgan et al. 1998; Boice et al. 1999; Hansen et al. 2001). The results were mixed, and there was no evidence of an exposure-response relationship. The Anttila et al. study also assessed exposure to PCE, dry-cleaning solvents, and unspecified mixtures of organic solvents and observed increased SIRs. Ruder et al. (2001) observed increased SMRs in 18 exposed dry-cleaning labor-union workers. IOM reviewed an additional case-control study (Kauppinen et al. 1995) and six mortality cohort studies of exposure to unspecified mixtures of organic solvents (McMichael et al. 1976; Pippard and Acheson 1985; Garabrant et al. 1988; Costantini et al. 1989; Acquavella et al. 1993; Fu et al. 1996). The numbers of exposed cases were small, and the results were mixed. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or other solvents and pancreatic cancer.

2008 Evaluation

The updated literature on TCE and pancreatic cancer included five cohort studies with cancer incidence or mortality data (Chang et al. 2003; Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007). Two studies of electronics workers (Chang et al. 2003; Sung et al. 2007) reported

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increased risk of pancreatic cancer in women, but the number of cases was small (16 in the two studies combined), and in one study TCE exposure was not distinguished from PCE exposure (Chang et al. 2003). Two studies of dry cleaners with data on PCE exposure and pancreatic cancer were identified; the SMR in a cohort study was 1.1 (95% CI, 0.7-1.5) (Blair et al. 2003), and the OR in a case-control study was 1.27 (95% CI, 0.90-1.80) (Lynge et al. 2006).

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and pancreatic cancer.

Hepatobiliary Cancer

IOM 2003 Conclusions

IOM (2003) did not find a consistent association between chronic exposure to TCE, PCE, or unspecified mixtures of organic solvents and an increased risk of hepatobiliary cancer (liver cancer and cancers of the gallbladder and biliary tract). IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and hepatobiliary cancer.

2008 Evaluation

The updated literature on TCE and hepatobiliary cancer included five cohort studies with incidence or mortality data (Morgan and Cassady 2002; Chang et al. 2003; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007) and one case-control study (Lee et al. 2003). The updated Danish study of workers with TCE exposure showed some increased SIRs for women (for example, 2.8 and a 95% CI of 1.13-5.80 for women employed at least 3 months; seven cases in exposed people), but most estimates were based on small numbers of cases in exposed people (Raaschou-Nielsen et al. 2003). The updated literature on PCE and hepatobiliary cancer included three cohort studies with cancer incidence or mortality data (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003) and two case-control studies (Lee et al. 2003; Lynge et al. 2006). Lynge et al. (2006) reported an RR of 0.76 (95% CI, 0.38-1.52) in a cohort of Nordic dry-cleaning workers. The case-control study by Lee et al. (2003) of a Taiwanese community exposed to solvents from an electronics factory reported an increased MOR for men (2.57; 95% CI, 1.21-5.46), but the exposure assessment was weak.

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and hepatobiliary cancer.

Lung Cancer

IOM 2003 Conclusions

IOM (2003) determined that the cohort and case-control studies of TCE and lung cancer were limited by exposure assessment and inadequate control for confounding factors, especially smoking. The studies generally did not show any increased risk, so the evidence regarding chronic exposure to TCE and lung cancer was considered inadequate/insufficient for determining whether an association exists. Although several studies of PCE exposure had positive results (Blair et al. 1990; Brownson et al. 1993; Anttila et al. 1995; Paulu et al. 1999; Pohlabeln et al. 2000; Ruder et al. 2001), IOM was unable to reach a

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consensus, because of some committee members' concerns regarding confounding by cigarette-smoking and the small numbers of exposed persons.

2008 Evaluation

The updated literature on TCE and lung cancer included seven cohort studies with lung-cancer incidence or mortality data (Hansen et al. 2001; Morgan and Cassady 2002; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007) and one case-control study (Lee et al. 2003). The new papers on PCE and lung cancer include three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003, 2005) and a case-control study (Lee et al. 2003). The updated Danish study of workers with TCE exposure (Raaschou-Nielsen et al. 2003) found increased SIRs for men and women (for example, 1.9 with a 95% CI of 1.48-2.35 for women employed at least 3 months), although there was no appearance of a trend with years of employment. Other studies did not report an increased risk with TCE exposure. The small number of studies of PCE exposure generally showed no increase in risk. However, the Blair et al. (2003) updated mortality analysis of dry cleaners showed increased SMRs, including an SMR of 1.5 (95% CI, 1.2-1.9) for workers with presumed medium or high PCE exposure. On the basis of the strengths of that study, including its size and exposure assessment, and the previous studies that had positive results, the committee determined that the evidence of an association was limited/suggestive.

- The updated literature on TCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to that solvent and lung cancer.
- On the basis of new data, the committee concludes that there is limited/suggestive evidence of an association between chronic exposure to PCE and lung cancer. This constitutes a new conclusion, in that a consensus was not reached in the 2003 IOM report.

Bone Cancer

IOM 2003 Conclusions

IOM (2003) identified one cohort study that reported on the association between occupational exposure to TCE and bone cancer (Blair et al 1998). On the basis of five exposed cases, the SMR was 2.1 (95% CI, 0.2-18.8). Two cohort studies reported on incidence of (Nielsen et al. 1996) or mortality from (Fu et al. 1996) bone cancer after occupational exposure to unspecified mixtures of organic solvents. Increased risks were reported, but a total of only seven exposed cases were identified. There were no studies of the association of PCE with bone cancer. Because of the small number of studies and the unstable estimates, IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or other solvents and bone cancer.

2008 Evaluation

The committee found two cohort studies that yielded no evidence of an association between occupational exposure to TCE and bone-cancer incidence (three cases in exposed people) (Sung et al. 2007) or bone-cancer mortality (no cases in exposed people) (Boice et al. 2006). In a mortality study of electronics workers with indeterminate exposure to TCE and PCE, the SMR was 1.63 (95% CI, 0.44-4.18) on the basis of four cases in exposed people (Chang et al. 2003). In an incidence study of the same population, the SIR in female workers (six cases in exposed people) was 1.28 (05% CI, 0.47-2.78) (Chang et al. 2005). Only one male worker was exposed.

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- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and bone cancer.

Soft-Tissue Sarcoma

IOM 2003 Conclusions

IOM (2003) could not draw any conclusion regarding an association between chronic exposure to solvents and soft-tissue sarcoma because of the lack of available studies (only one study was identified).

2008 Evaluation

The updated literature on soft-tissue sarcoma included a cancer-mortality study (Chang et al. 2003) and an incidence analysis (Chang et al. 2005) of a cohort of workers in a Taiwanese electronics factory exposed to TCE and PCE. The mortality analysis did not find any deaths from connective-tissue and other soft-tissue cancer. The incidence study found an increased but imprecise SIR for connective-tissue and other soft-tissue cancer in men (1.43; 95% CI, 0.29-4.17); no increase in risk was found in women.

- The committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and soft-tissue sarcoma. This constitutes a new conclusion, in that no conclusion was drawn in the 2003 IOM report.

Melanoma

IOM 2003 Conclusions

IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or unspecified mixtures of solvents and melanoma.

2008 Evaluation

The updated literature on TCE and melanoma included seven cohort studies with cancer incidence or mortality data (Hansen et al. 2001; Morgan and Cassady 2002; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007). The updated publications on PCE and melanoma included three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003). The study by Morgan and Cassady found a significantly increased SIR for residents in a community exposed to drinking water contaminated with TCE and PCE (SIR, 1.42; 99% CI, 1.13-1.77), but the authors attributed the observation to the high socioeconomic status (SES) of the residents of the community. The incidence patterns of other cancers in the community—especially those of lung, colorectal, and uterine cancer—appeared to be consistent with and supportive of the authors' explanation. None of the other studies reported an increased risk of melanoma in those exposed to TCE or PCE.

- The updated literature on TCE and PCE continues to support a conclusion that there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to these solvents and melanoma.

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Nonmelanoma Skin Cancer

IOM 2003 Conclusions

IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or unspecified mixtures of solvents and non-melanoma skin cancer.

2008 Evaluation

No studies of TCE or PCE and nonmelanoma skin cancer were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and nonmelanoma skin cancer.

Breast Cancer

IOM 2003 Conclusions

IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or unspecified mixtures of organic solvents and breast cancer. Results of occupational-cohort studies of breast-cancer risk were mixed (Garabrant et al. 1988; Shannon et al. 1988; Blair et al. 1990, 1998; Anttila et al. 1995; Morgan et al. 1998; Boice et al. 1999; Hansen et al. 2001; Ruder et al. 2001). Those studies were limited by exposure misclassification, poor control for confounding, and low statistical power due to small numbers. Information on reproductive risk factors was available in the three case-control studies (including one community study), and their results showed positive associations between exposure to PCE and unspecified mixtures and breast cancer (Aschengrau et al. 1998; Hansen 1999; Band et al. 2000). The one case-control study of male breast cancer observed no association with exposure to solvents.

2008 Evaluation

The committee identified five new or updated occupational-cohort studies that assesse breast-cancer incidence or mortality associated with TCE or PCE (Blair et al. 2003; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Sung et al 2007). The reported SIRs and SMRs ranged from 1.1 to 1.2 in most studies. Sung et al. (2007) found an SIR of 1.38 (95% CI, 1.11-1.70) in electronics workers employed before June 1974 and exposed to TCE and mixed solvents. Chang et al. (2003) reported an increased incidence of breast cancer in employees exposed to TCE and PCE at an electronics factory in Taiwan. The highest SIR was associated with 5-10 years of exposure (SIR, 1.69; 95% CI, 1.02-2.64), but the association was stronger for more recent employment than for employment 5 or 10 years before diagnosis. In an update of their 1998 case-control study in a community exposed to PCE-contaminated drinking water, Aschengrau et al. (2003) continued to see increased, but attenuated, associations with breast cancer (ORs ranged from 0.9 to 1.9 depending on exposure). There was no clear evidence of the appropriate latency period (Vieira et al. 2005). In a community-based cohort study of PCE and TCE contamination of the public drinking-water supply, the SIR was consistent with that in the occupational studies (1.09; 99% CI, 0.97-1.21) (Morgan and Cassady 2002). The Aschengrau et al. study was the only new study that controlled for confounding by reproductive risk factors. No new studies included cases of male breast cancer.

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- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE and female breast cancer.
- On the basis of the new Aschengrau et al. (2003) study, the committee concludes that there is limited/suggestive evidence of an association between chronic exposure to PCE and breast cancer. This conclusion constitutes a change in the one drawn by IOM (2003).

Cervical Cancer

IOM 2003 Conclusions

IOM (2003) identified five cohort studies with data on the incidence of or mortality from cervical cancer after TCE exposure (Anttila et al. 1995; Blair et al. 1998; Morgan et al. 1998; Boice et al. 1999; Hansen et al. 2001). All had fewer than five exposed cases. Increased risks were observed in three studies that used biologic monitoring (Anttila et al. 1995; Blair et al. 1998; Hansen et al. 2001), and two of the three reported an exposure-response relationship (Anttila et al. 1995; Blair et al. 1998). The followup in the other two studies was not long enough to observe any deaths from cervical cancer (Morgan et al. 1998; Boice et al. 1999). Because of the concern about lack of control for SES and exposure to the human papilloma virus, IOM was not able to come to a consensus opinion on TCE exposure and cervical cancer.

The Anttila et al. (1995) study observed an association between exposure to PCE and incidence of cervical cancer. Two mortality cohorts of dry-cleaning workers also observed increased risks, but there was no evidence of an exposure-response relationship (Blair et al. 1990; Ruder et al. 2001). A study of Swedish patients with solvent-related disorders reported an increased SMR for cervical cancer (Berlin et al. 1995). IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to PCE or unspecified mixtures of organic solvents and cervical cancer.

2008 Evaluation

The updated literature on TCE exposure and cervical cancer included several occupational-cohort studies with incidence data (Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Sung et al. 2007). Raaschou-Nielsen et al. (2003) observed an SIR of 1.9 (95% CI, 1.4-2.4) in Danish workers; however, there was no evidence of an exposure-response relationship. The SIR in over 300 exposed electronics workers in Taiwan was not increased (Sung et al. 2007). In a mortality study of electronics manufacturing workers exposed to TCE and PCE, an association with cervical cancer was not observed (Chang et al. 2003). In an incidence study of the same population, however, there was some indication of an exposure-response relationship (Chang et al. 2005). There was no association with cervical cancer in an incidence study of a community exposed to TCE and PCE in drinking water (Morgan and Cassady 2002). A cohort study of dry cleaners exposed to PCE and other dry-cleaning solvents found an increased SMR for cervical cancer, but there was no evidence of an exposure-response relationship. A case-control study of Nordic dry cleaners did not observe an association between PCE and cervical cancer in 36 cases in exposed people (Lynge et al. 2006).

- The committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between chronic exposure to TCE or PCE and cervical cancer. This constitutes a new conclusion for TCE, in that a consensus was not reached in the 2003 IOM report.

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Ovarian and Uterine Cancer

IOM 2003 Conclusions

IOM (2003) reviewed four cohort studies with incidence or mortality data on ovarian or uterine cancer and exposure to TCE, PCE, or mixed solvents (Blair et al. 1990; Morgan et al. 1998; Boice et al. 1999; Hansen et al. 2001). No studies showed meaningful increases in the risk of those cancers. Furthermore, the number of cases in exposed people was extremely small: nine or fewer of either type in each study. Thus, IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and ovarian or uterine cancer.

2008 Evaluation

The updated literature for TCE and PCE exposure and ovarian and uterine cancer included several occupational-cohort studies with incidence or mortality data (Blair et al. 2003; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Sung et al. 2007). With the exception of increased but unstable rates of uterine and ovarian cancer reported in the incidence study of Taiwanese electronics workers (Chang et al. 2005), the studies did not indicate evidence of an association with TCE or PCE. Numbers of exposed cases in all studies were small. In a study of a community exposed to TCE and PCE in the public drinking-water supply, the SIRs for ovarian and uterine cancer were 1.16 (99% CI, 0.85-1.53) and 1.35 (99% CI, 106-1.70), respectively (Morgan and Cassady 2002).

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and ovarian or uterine cancer.

Prostate Cancer

IOM 2003 Conclusions

IOM (2003) reviewed nine cohort studies with incidence or mortality data on an association between TCE and prostate cancer (Wilcosky et al. 1984; Greenland et al. 1994; Anttila et al. 1995; Blair et al. 1998; Morgan et al. 1998; Boice et al. 1999; Ritz 1999; Hansen et al. 2001). The results were mixed. Two cohort studies of dry-cleaning workers did not find an association between PCE and dry-cleaning solvents and prostate cancer (Blair et al. 1990; Ruder et al. 1994). Five cohort studies assessed exposure to unspecified mixtures of organic solvents and incidence of or mortality from prostatic cancer (Morgan et al. 1981; Matanoski et al. 1986; Garabrant et al. 1988; Greenland et al. 1994; Anttila et al. 1995; Boice et al. 1999). With the exception of the Anttila et al. study, which reported an SIR of 1.38 (95% CI, 0.73-2.35) in all workers (13 cases in exposed people) and an SIR of 3.57 (95% CI, 1.54-7.02) in workers with over 20 years of exposure (eight cases), the risks were not increased. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and prostate cancer.

2008 Evaluation

The updated literature on occupational exposure to TCE and PCE and prostate cancer includes two cohort studies (Raaschou-Nielsen et al. 2003; Boice et al. 2006) and one case-control study (Krishnadasan et al. 2007) of workers exposed to TCE, one cohort study of dry cleaners exposed to PCE and dry-cleaning solvents (Blair et al 2003), and one study of electronics workers exposed to TCE and PCE (Chang et al. 2003). Positive risks were observed only for TCE in the Krishnadasan study; ORs for low-

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moderate exposure and high exposure were 1.3 (95% CI, 0.81-2.1) and 2.1 (95% CI, 1.2-3.9), respectively. A study of a community exposed to TCE and PCE in drinking water reported an SIR of 1.11 (99% CI, 0.98-1.25) (Morgan and Cassady 2002).

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE and prostate cancer.

Bladder Cancer

IOM 2003 Conclusions

IOM (2003) reviewed seven cohort studies of occupational exposure to TCE that evaluated bladder-cancer incidence or mortality and one case-control study and concluded that there was insufficient/inadequate evidence to determine whether an association exists. That conclusion was based on weak and imprecise associations, low statistical power, and probable exposure misclassification. However, IOM concluded that there is limited/suggestive evidence of an association between chronic exposure to PCE and dry-cleaning solvents and bladder cancer. That conclusion was based on cohort studies (Blair et al. 1990; Ruder et al. 2001) and case-control studies (Schoenberg et al. 1984; Smith et al. 1985; Teschke et al. 1997; Pesch et al. 2000a) of dry cleaners that found increased risks of bladder cancer. In addition, a community study of PCE-contaminated drinking water found evidence of a positive exposure-response relationship (Aschengrau et al. 1993). The evidence of an association with chronic exposure to unspecified mixtures of organic solvents was also determined to be limited/suggestive on the basis of consistent positive findings in four case-control studies (Schoenberg et al. 1984; Morrison et al. 1985; Jensen et al. 1987; Pesch et al. 2000b) and cohort studies of painters (Steenland and Palu 1999) and aircraft workers (Garabrant et al. 1988).

2008 Evaluation

The committee identified four new cohort studies of occupational groups potentially exposed to TCE (Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007) and one in which exposures to TCE and to PCE were not distinguished (Chang et al. 2003). The results were inconsistent. In the continued followup study of dry-cleaning workers (Blair et al 2003), the SMR for bladder cancer was increased at 1.3 (95% CI, 0.7-2.4) but lower than in the first report. A new cohort study of dry cleaners found a positive association between exposure and bladder cancer with some evidence of a positive exposure-response relationship (Lynge et al. 2006). A study of a community exposed to TCE and PCE in the public drinking-water supply found no evidence of an increased risk of bladder cancer after exposure (Morgan and Cassady 2002). There were no new studies of unspecified mixtures.

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE and bladder cancer. The evidence on PCE and mixtures of organic solvents continues to support a conclusion that there is limited/suggestive evidence of an association between chronic exposure to PCE or mixtures of organic solvents and bladder cancer.

Kidney Cancer

IOM 2003 Conclusions

For TCE, positive associations with kidney cancer were suggested by three studies (Henschler et

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al. 1995; Vamvakas et al. 1998; Pesch et al. 2000b). On the basis of an apparent cluster of cases, Henschler et al. (1995) conducted a retrospective cohort study in a cardboard factory in Germany to examine the association between TCE exposure and renal cell cancer. The study group included 169 men who had been exposed to TCE for at least 1 year between 1956 and 1975. The study reported incident kidney cancer among five exposed men (RR of 7.9; 95% CI, 2.59-8.59). A case-control study in the same region of Germany reported an elevated risk of kidney cancer (OR of 10.8; 95% CI, 3.36-34.7) (Vamvakas et al. 1998). The findings from the German cohort study raised interest because of the long employment period (an average of 34 years) and the potential for high exposure to TCE. Another case-control study in multiple regions of Germany reported an increased risk of kidney cancer among men with presumed substantial TCE exposure (Pesch et al. 2000b). Collectively, the IOM committee judged the studies insufficient for drawing conclusions because they had small sample sizes, one had poor exposure data (self reports in Vamvakas et al. 1998), one was a cluster investigation (Henschler et al. 1995), and the results of the Pesch et al. (2000b) study were not persuasive.

However, the results of several well-conducted epidemiologic studies of PCE (McCredie and Stewart 1993; Mandel et al. 1995; Pesch et al. 2000b) warranted a conclusion that there was limited/suggestive evidence of an association between chronic exposure to PCE and kidney cancer. IOM was unable to reach a consensus conclusion on unspecified mixtures of organic solvents.

2008 Evaluation

The updated literature on TCE and kidney cancer included six cohort studies with cancer incidence or mortality data (Morgan and Cassady 2002; Chang et al. 2003; Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007) and two case-control studies (Bruning et al. 2003; Charbotel et al. 2006). The updated literature on PCE and kidney cancer included three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003) and two case-control studies (Bruning et al. 2003; Lynge et al. 2006). Several of the cohort studies of TCE reported an increased risk of kidney cancer, including in some the appearance of a dose-response relationship on the basis of years of employment or presumed higher exposure levels. For example, Raaschou-Nielsen et al. (2003) reported an SIR of 1.6 (95% CI, 1.1-2.3) in men employed for 5 years or more; Zhao et al. (2005) found an SIR of 4.90 (95% CI, 1.23-19.6) for an estimated high level of TCE exposure of aerospace workers. The results were often based on a relatively small number of exposed persons and varied quality of exposure data and methods of exposure assessment. The few studies of PCE largely showed no increase in risk, although most effect estimates are imprecise because of the very small number of exposed cases.

- On the basis of the available data, the committee concludes that there is limited/suggestive evidence of an association between chronic exposure to TCE or PCE and kidney cancer. In the case of TCE, that conclusion constitutes a change in the one drawn by IOM (2003).
- Because consensus was not reached on a characterization of the data on mixtures of organic solvents and kidney cancer, the committee performed its own evaluation of the data in the IOM (2003) report. The committee concluded that reports of positive associations in multiple studies, even in the context of study limitations and negative studies, were sufficient to state that the evidence of an association between mixtures of organic solvents and kidney cancer is limited/suggestive.

Cancer of the Brain or Central Nervous System

IOM 2003 Conclusions

Some studies found some positive associations between TCE and brain cancer (Heineman et al. 1994; Rodvall et al. 1996; Ritz 1999), but IOM (2003) judged that the cohort and case-control studies

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were limited by confounding by other exposures, imprecise effect estimates, and lack of specificity of brain-tumor type. Thus, the evidence on chronic exposure to TCE and brain or central nervous system (CNS) cancer was characterized as inadequate/insufficient to determine whether an association exists. With regard to PCE, no consistent pattern of increased relative risk was found, so the evidence was judged to be inadequate/insufficient to determine whether there is an association between chronic exposure to PCE and brain or CNS cancer. Although some positive associations were reported in studies of unspecified mixtures of solvents, the evidence was considered inadequate/insufficient to determine whether an association exists.

2008 Evaluation

The updated literature on TCE and brain or CNS cancer included several cohort studies with cancer incidence or mortality data (Hansen et al. 2001; Morgan and Cassady 2002; Chang et al. 2003, 2005; Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006; Sung et al. 2007). The updated literature on PCE and brain or CNS cancer included three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003). The studies of TCE did not show an increase in risk except the Morgan and Cassady study of drinking water contaminated with TCE and perchlorate, which reported a weakly increased SIR of 1.54 (95% CI, 0.96-2.31). The small number of studies of PCE generally showed no increase in risk.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and brain or CNS cancer.

Non-Hodgkin Lymphoma

IOM 2003 Conclusions

IOM (2003) reviewed two cohort studies that involved exposure to TCE (Wilcosky et al. 1984; Blair et al. 1998) and that suggested an increased risk of dying from non-Hodgkin lymphoma. In the Wilcosky et al. study, rubber workers were exposed to numerous other chemicals. The Blair et al. study found no evidence of a dose-response relationship with respect to mortality and no association in relation to incidence. A case-control study showed a strong association between TCE and non-Hodgkin lymphoma, but IOM judged it highly probable that the RRs were overstated. Thus, IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or unspecified mixtures of solvents and non-Hodgkin lymphoma. Statistical fluctuation was cited as an important reason for drawing that conclusion.

2008 Evaluation

The updated literature on TCE and non-Hodgkin lymphoma included four cohort studies with cancer incidence or mortality data (Morgan and Cassady 2002; Raaschou-Nielsen et al. 2003; Zhao et al. 2005; Boice et al. 2006) and two case-control studies (Miligi et al. 2006; Seidler et al 2007). In an occupational-cohort study, male Danish workers exposed to TCE had a weakly increased risk of non-Hodgkin lymphoma, and there appeared to be a dose-response relationship—the SIRs for those employed for less than 1 year, for 1-4.9 years, and for 5 years or more were 1.1 (95% CI, 0.7-1.6), 1.3 (95% CI, 0.9-1.8), and 1.4 (95% CI, 0.9-2.0), respectively (Raaschou-Nielsen et al. 2003). A similar pattern was observed in female workers in the same study. The case-control study by Seidler et al. (2007) found that German workers exposed to TCE at concentrations greater than 35 ppm/year had an increased risk of B-cell non-Hodgkin lymphoma (OR, 2.3; 95% CI, 1.0-5.3). The updated literature on PCE and non-Hodgkin lym-

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phoma included two cohort studies (Morgan and Cassady 2002; Blair et al. 2003) and three case-control studies (Lynge et al. 2006; Miligi et al. 2006; Seidler et al. 2007). None of the studies reported an association between exposure to PCE and non-Hodgkin lymphoma.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and non-Hodgkin lymphoma.

Hodgkin Disease

IOM 2003 Conclusions

Because of the small numbers of exposed cases in the available studies and a lack of specific or validated exposure-assessment information in the studies reviewed, IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE, PCE, or unspecified mixtures of solvents and Hodgkin disease.

2008 Evaluation

The updated literature on TCE and Hodgkin disease included five cohort studies with cancer incidence or mortality data (Hansen et al. 2001; Morgan and Cassady 2002; Chang et al. 2003; Raaschou-Nielsen et al. 2003; Boice et al. 2006) and one case-control study (Seidler et al. 2007). The updated literature on PCE and Hodgkin disease included three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003) and one case-control study (Seidler et al. 2007). The newer studies were still characterized by small numbers of exposed cases and provided no persuasive evidence of an association between TCE or PCE and Hodgkin disease.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and Hodgkin disease.

Multiple Myeloma

IOM 2003 Conclusions

Given a lack of positive findings, IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and multiple myeloma. A number of studies of painters found an increased risk of multiple myeloma after exposure to solvent mixtures. Thus, IOM concluded that there was limited/suggestive evidence of an association between chronic exposure to solvents (as observed in studies of painters) and multiple myeloma.

2008 Evaluation

The updated literature on TCE and multiple myeloma included two cohort studies with cancer incidence or mortality data (Raaschou-Nielsen et al. 2003; Boice et al. 2006) and one case-control study (Seidler et al. 2007). None of the three studies suggested an association between exposure to TCE and multiple myeloma. The SIR in male Danish workers who held jobs with TCE exposure for at least 3 months was 1.1 (95% CI, 0.70-1.52). The updated literature on PCE and multiple myeloma included one

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cohort study (Blair et al. 2003) and one case-control study (Seidler et al. 2007). Both studies had small numbers of exposed cases (seven or fewer) and found no persuasive evidence of an association.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and multiple myeloma. IOM's conclusion that there is limited/suggestive evidence of an association between chronic exposure to solvents and multiple myeloma also remains unchanged.

Adult Leukemia

IOM 2003 Conclusions

Owing to the small number of relevant studies and the lack of consistently positive findings, IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and adult leukemia. However, the findings on unspecified mixtures of organic solvents and adult leukemia showed increased RRs, including two studies that found evidence of a dose-response relationship. IOM concluded that there was limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and adult leukemia.

2008 Evaluation

The updated literature on TCE and adult leukemia included five cohort studies with cancer incidence or mortality data (Morgan and Cassady 2002; Chang et al. 2003; Raaschou-Nielsen et al. 2003; Boice et al. 2006; Sung et al. 2007) and one case-control study (Seidler et al. 2007). The updated literature on PCE and adult leukemia included three cohort studies (Morgan and Cassady 2002; Blair et al. 2003; Chang et al. 2003) and one case-control study (Seidler et al. 2007). The study by Morgan and Cassady (2002) did not find any change in leukemia incidence in residents of a community exposed to drinking water contaminated with TCE and PCE (SIR, 1.02; 99% CI, 0.74-1.35). The risk of adult leukemia was not linked to exposure to TCE or PCE in any of the other newly identified studies.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and adult leukemia. IOM's conclusion that there is limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and adult leukemia also remains unchanged.

Myelodysplastic Syndromes

IOM 2003 Conclusions

All the studies reviewed in the IOM (2003) report were case-control studies. None focused specifically on TCE or PCE. Most of the studies evaluated unspecified mixtures of organic solvents and relied on self-reported exposures. All but one study found consistently positive ORs. IOM concluded that there was limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and myelodysplastic syndromes but drew no conclusions about individual solvents.

2008 Evaluation

No new studies focusing on TCE or PCE and myelodysplastic syndromes were identified.

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- The committee concludes there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and myelodysplastic syndromes. IOM's conclusion that there was limited/suggestive evidence of an association between chronic exposure to unspecified mixtures of organic solvents and myelodysplastic syndromes remains unchanged.

Childhood Leukemia

IOM 2003 Conclusions

IOM (2003) was unable to reach a consensus conclusion regarding the relationship between exposure to organic solvents and childhood leukemia. Several studies found positive associations with exposure to solvents. Some studies were limited by misclassification bias related to self-reporting of exposure, and some were limited by looking at all childhood leukemia or focusing on specific cell types. Because of these factors, some IOM committee members believed that the evidence fulfilled the category of inadequate/insufficient evidence to determine whether an association exists; others believed that it was limited/suggestive of an association.

2008 Evaluation

The updated literature on TCE and childhood leukemia included one cohort study with incidence data (Morgan and Cassady 2002) and one case-control study (Costas et al. 2002). Updated literature on PCE and childhood leukemia included one cohort study with incidence data (Morgan and Cassady 2002) and two case-control studies (Costas et al. 2002; Infante-Rivard et al. 2005). The cohort study by Morgan and Cassady (2002) did not find any change in the incidence of childhood leukemia in residents of a community exposed to drinking water contaminated with TCE and PCE (SIR, 1.09; 99% CI, 0.38-2.31). The case-control study found no association between maternal occupational exposure to PCE and leukemia in offspring (Infante-Rivard et al. 2005). The OR for maternal PCE exposure from 2 years before pregnancy to birth was 0.96 (95% CI, 0.41-2.25), and the OR for maternal PCE exposure during pregnancy was 0.84 (95% CI, 0.30-2.34). The case-control study by Costas et al. (2002) suggested a dose-response relationship between cumulative exposure to water from municipal drinking water contaminated with TCE, PCE, and other chemicals and childhood leukemia. However, the interpretation of such a finding is limited by the small number of exposed cases (10) and the uncertainty in exposure assessment.

- On the basis of the available literature, the committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between TCE or PCE and childhood leukemia. This constitutes a new conclusion, in that consensus was not reached in the 2003 IOM report.

Childhood Neuroblastoma

IOM 2003 Conclusions

A case-control study found few associations between maternal or paternal occupational exposure to solvents, including TCE or PCE, and neuroblastoma in offspring (De Roos et al. 2001). IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and neuroblastoma.

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2008 Evaluation

No new studies on solvent exposure and neuroblastoma were found.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and neuroblastoma.

Childhood Brain Cancer

IOM 2003 Conclusions

One of two case-control studies found some associations between maternal (OR, 0.9-3.2) or paternal (OR, 0.4-2.3) occupational exposure to solvents (as a group) and childhood brain cancer in offspring (Cordier et al. 1997). IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and childhood brain cancer.

2008 Evaluation

A study by Morgan and Cassady (2002) study did not find an association between community exposure to water contaminated with TCE and PCE and childhood brain cancer.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and childhood brain cancer.

Noncancer End Points

Aplastic Anemia

IOM 2003 Conclusions

The IOM (2003) report included a total of three studies (all case-control studies) of organic solvents (other than benzene) and aplastic anemia. One study reported a significantly increased risk, and the other two did not find an association. None of the three studies focused on TCE or PCE. On the basis of results, IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to specific organic solvents (other than benzene) or solvent mixtures and aplastic anemia.

2008 Evaluation

No additional studies of TCE or PCE and aplastic anemia were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and aplastic anemia.

Congenital Malformations

IOM 2003 Conclusions

A small number of studies that examined parental solvent exposure before or during pregnancy

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did not find a pattern of association except for a study of gastroschisis that reported several increased but imprecise ORs (Torfs et al. 1996). IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and congenital malformations.

2008 Evaluation

A community study that assessed residential proximity to a TCE-emitting facility did not find an overall association with congenital heart defects but reported an association with presumed TCE exposure among older mothers (among exposed mothers 38 years or older) and such defects (OR, 4.1; 95% CI, 1.5-11.2) (Yauck et al. 2004). A case-control study of maternal occupational exposure to organic solvent mixtures found an increased but very imprecise OR (9.2; 95% CI, 2.5-35.3) for oral clefts among offspring (Chevrier et al. 2006).

- There continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and congenital malformations.

Male Fertility

IOM 2003 Conclusions

Many studies have investigated potential paternal occupational exposure to solvents and male infertility. They used occupation or industry as a surrogate for solvent exposure. IOM (2003) reviewed only studies that had a better characterization of solvent exposure. Nonetheless, only one study performed a specific assessment of TCE or PCE exposure. The five studies reviewed by IOM that examined male solvent exposure and effects that persisted after cessation of exposure had inconsistent results, including some associations with poorer semen quality. Most studies tended to be small and recruited men from infertility clinics or couples seeking an infertility consultation. Others reported inconsistent associations between solvents and indirect measures of fertility, including hormone concentrations and time to pregnancy. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents and male infertility.

2008 Evaluation

A study of men occupationally exposed to solvents (painters and millwrights) reported an association between increasing follicle-stimulating hormone and indexes of exposure to all solvents and to chlorinated solvents (Luderer et al. 2004). No association with luteinizing hormone concentration or time to pregnancy was found.

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between chronic exposure to TCE or PCE and male infertility.

Female Fertility

IOM 2003 Conclusions

A few studies have evaluated miscellaneous solvent exposure, not TCE or PCE specifically, in relation to fecundability (ability to become pregnant), typically measured as time to pregnancy. In those studies, a lower hazard ratio means that conception was less likely in exposed than in unexposed women.

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Reduced fecundability was found in female printing-industry workers (fecundability ratio, 0.52; 95% CI, 0.28-0.99) (Plenge-Bonig and Karmaus 1999), women in jobs determined by biologic monitoring to have high solvent exposure (fecundability ratio, 0.41; 95% CI, 0.27-0.62) (Sallmen et al. 1995), and semiconductor-industry workers exposed to ethylene glycol ethers (fecundability ratio, 0.37; 95% CI, 0.11-1.19) (Eskenazi et al. 1995). One additional study used subfertility, the inability to conceive within 1 year, as the outcome measure and found an increased risk in female semiconductor workers (OR, 4.6; 95% CI, 1.6-13.3) (Correa et al. 1996). The only reported estimates of effects of TCE and PCE exposure come from the study by Sallmen et al. (1995), who found fecundability ratios of 0.61 (95% CI, 0.28-1.33) and 0.69 (95% CI, 0.31-1.52), respectively, consistent with the pattern for solvents in general. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and female infertility after cessation of exposure. It drew no conclusions about the evidence on concurrent exposure to solvents and effects on fertility, because its review focused on fertility risks to veterans after deployment (after cessation of exposure).

2008 Evaluation

No additional studies addressing female infertility were identified after the 2003 IOM report. The committee evaluated the studies included in that review (see above) to draw conclusions about the evidence on concurrent exposure to solvents and female fertility.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to TCE or PCE and female infertility after exposure cessation; this agrees with IOM (2003).
- The committee concludes that there is limited/suggestive evidence of an association between *concurrent* exposure to solvents and female infertility, which was not addressed in the 2003 IOM report.

Pregnancy Outcomes (Maternal Exposure)

IOM 2003 Conclusions

The IOM (2003) report focused on delayed or chronic effects of exposure that are manifested in adverse pregnancy outcomes after cessation of exposure. IOM summarized the available evidence, which was primarily on exposure during pregnancy. Preconception exposure of women and later adverse pregnancy outcomes were not addressed in any of the studies. A number of studies have suggested that maternal exposure to solvents in general and dry-cleaning work in particular are associated with miscarriage. Four studies that reported some evidence of an association between maternal dry-cleaning employment and miscarriage were cited (Kyyronen et al. 1989; Ahlborg 1990; Olsen et al. 1990; Doyle et al. 1997), and a greater number of other reports suggested an association with other sources of occupational solvent exposure, including work in semiconductor plants, shoe factories, and laboratories. Although consistent among studies, the quality of exposure assessment in all the studies is limited, and there are difficulties to identifying and documenting the occurrence of miscarriage accurately. Few studies have considered other pregnancy outcomes (such as preterm birth and fetal growth restriction), and they yielded little support of an association. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between maternal preconception exposure to TCE, PCE, or other solvents reviewed and miscarriage or other adverse pregnancy outcomes. It drew no conclusions about the evidence on exposure during pregnancy, because its review was focused on risks to veterans of war and it was assumed that no female soldiers were pregnant while deployed.

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2008 Evaluation

No additional studies of maternal solvent exposure and miscarriage were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between maternal preconception exposure to TCE or PCE and miscarriage or other adverse pregnancy outcomes (such as preterm birth and fetal growth restriction).
- The committee concludes there is inadequate/insufficient evidence to determine whether an association exists between maternal solvent exposure during pregnancy and preterm birth or fetal growth restriction.
- The committee concludes that there is limited/suggestive evidence of an association between maternal exposure to PCE (and to solvents in general) during pregnancy and miscarriage.

Pregnancy Outcomes (Paternal Exposure)

IOM 2003 Conclusions

Four studies that addressed paternal exposure to solvents and pregnancy outcomes were identified. Scattered positive associations were reported but no consistent evidence of an association with miscarriage, the most frequently studied pregnancy outcome. The studies tended to be small, relied on self-reported exposure, and had indirect assessment of solvent exposure (and not specifically exposure to TCE or PCE). The one study of dry-cleaning workers (Eskenazi et al. 1991) did not find a positive association. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between paternal exposure to TCE, PCE, or other solvents reviewed and miscarriage or other adverse pregnancy outcomes.

2008 Evaluation

No additional studies of paternal solvent exposure and pregnancy outcomes were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between paternal exposure to TCE, PCE, and other solvents and adverse pregnancy outcomes.

Cardiovascular Effects

IOM 2003 Conclusions

IOM found a number of studies of short-term effects of acute, relatively high-dose exposure to solvents. Effects tended to be exacerbation of symptoms of underlying cardiovascular disease that were reversible. Many cohort mortality studies of solvent-exposed workers have been conducted, but they were limited by the healthy-worker effect to various degrees, and none provided much support of increased mortality from cardiovascular disease associated with solvent exposure. The magnitude of solvent exposure encountered in occupational settings would be substantially greater than that in the community, and the solvents would be inhaled or absorbed dermally, unlike the ingestion found in community studies. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to specific solvents and cardiovascular disease.

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2008 Evaluation

Several studies have extended the followup of dry-cleaning workers (Ruder et al. 2001; Blair et al. 2003) and continue to generate evidence of no increase in mortality from cardiovascular disease.

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and cardiovascular disease.

Hepatic Effects

IOM 2003 Conclusions

Liver function. Acute, high-level TCE exposure has effects on liver function, as does exposure to other solvents, but there is little evidence of lingering effects of chronic low-level exposure. Studies of workers with chronic exposure to solvents (such as painters and dry-cleaning workers) have not shown abnormal enzyme concentrations indicative of deleterious effects on liver function. Mild increases in hepatic enzymes have been noted in a few studies, but the studies did not differentiate past and current, continuous solvent exposure, so it was not possible to distinguish long- and short-term effects.

Hepatic steatosis. Acute, high-level exposure to such solvents as chloroform and carbon tetrachloride causes injury to the liver. Case series and some small epidemiologic studies of petrochemical and dry-cleaning workers indicate that a variety of solvents can cause fatty changes in the liver (steatosis) and that the problem persists after exposure ceases (Dossing et al. 1983; Redlich et al. 1990; Cotrim et al. 1999). The association seems clear for acute effects of high-level solvent exposure, but the dose-response gradient and the temporal course of exposure, response, and potential reversal are not well established.

Cirrhosis. Except for some case reports of cirrhosis associated with high-level solvent exposure, there are few informative data on solvent exposure and cirrhosis. Some studies of solvent-exposed workers have suggested an increased risk of cirrhosis, but the substantial influence of alcohol use and viral exposure on risk leaves open the potential for serious confounding.

- IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and chronic changes in hepatic function or cirrhosis.
- IOM concluded there was limited/suggestive evidence of an association between chronic exposure to solvents in general and hepatic steatosis that "could persist" after cessation of exposure.

2008 Evaluation

Extended followup of dry-cleaning workers continues to show no increased risk of hepatic effects (Ruder et al. 2001; Blair et al. 2003).

- The committee concludes that there continues to be inadequate/insufficient evidence determine whether an association exists between solvent exposure and changes in hepatic function or cirrhosis and limited/suggestive evidence of an association between chronic exposure to solvents and hepatic steatosis, which may persist after cessation of exposure.

Gastrointestinal Effects

IOM 2003 Conclusions

The only gastrointestinal effect that has been investigated as a possible consequence of solvent

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exposure is chronic pancreatitis. It is a persistent inflammatory condition strongly affected by alcohol consumption. One study examined a variety of occupational exposures in relation to chronic pancreatitis (McNamee et al. 1994), including solvent-exposed occupations, but found only an imprecise suggestion of a possible association with high cumulative exposure to chlorinated solvents. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and chronic pancreatitis.

2008 Evaluation

No additional studies of solvent exposure and gastrointestinal effects were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and gastrointestinal effects.

Renal Effects

IOM 2003 Conclusions

Several renal diseases have been examined in epidemiologic studies, including such specific conditions as acute tubular necrosis and chronic glomerulonephritis and such nonspecific conditions as indicators of renal function and end-stage renal disease. Studies of the effects of short-term and long-term solvent exposure on renal function below the threshold of clinical disease have yielded some support of an association between exposure to high concentrations of solvents and acute tubular necrosis. A series of case-control studies have evaluated chronic glomerulonephritis, an immune-mediated disease, in relation to solvent exposure and have yielded mixed evidence of an association, including several reasonably strong positive studies showing dose-response gradients. None of the studies addressed TCE or PCE directly; the closest any came was one that reported an association with "degreasing agents" (Porro et al. 1992). IOM concluded that there was limited/suggestive evidence of an association between exposure to solvent mixtures and chronic glomerulonephritis. Several studies have addressed the effect of solvent exposure on indicators of renal function; they used various magnitudes of exposure and had varied quality of exposure assessment. One study (Steenland et al. 1990) reported a fairly strong association between degreasing solvents and end-stage renal disease.

2008 Evaluation

No new studies of solvent exposure and glomerulonephritis were identified. An occupational-cohort study of aircraft-maintenance employees implicates solvents and points toward TCE more than PCE in relation to end-stage renal disease (Radican et al. 2006). Retrospective exposure assessment was detailed and identified greater than two-fold increases in risk with higher exposure. Study of renal function in workers exposed to TCE showed decrements in renal function in the clinically normal range (Green et al. 2004). The additional evidence strengthens the quantity and quality of information on TCE.

- The committee concludes that there continues to be limited/suggestive evidence of an association between mixed solvent exposure and chronic glomerulonephritis but inadequate/insufficient evidence to determine whether an association exists specifically between TCE or PCE and chronic glomerulonephritis.

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Systemic Rheumatic Disease

IOM 2003 Conclusions

Scleroderma, an autoimmune disease resulting in abnormal growth of connective tissue, has been addressed in several epidemiologic studies in relation to occupational solvent exposure, most of which relied on job-exposure matrices to infer solvent exposure. A report by Nietert et al. (1998) found an OR of 3.3 (95% CI, 1.0-10.3) for TCE and scleroderma in men but not in women, who have a higher overall risk of this disease. Other small, relatively crude studies with limited exposure assessment have generated mixed findings regarding the existence of an association. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between solvent exposure and scleroderma.

2008 Evaluation

Since the IOM review, there have been four studies of solvent exposure and scleroderma that used more sophisticated methods of assessing exposure. A case-control study of women in Michigan considered self-reported and expert-confirmed exposure and found a two-fold increased risk associated with TCE exposure but no association with PCE exposure (Garabrant et al. 2003). A case-control study in France found markedly increased risk of scleroderma associated with solvents, which challenges the plausibility of the findings, but the list of implicated solvents included TCE (Diot et al. 2002). A small study of women in Hungary found an increased risk associated with solvent exposure (Czirják and Kumanovics 2002). Finally, a case-control study in Italy found that solvent exposure increased the risk of scleroderma by a factor of 2.5 (Bovenzi et al. 2004).

- On the basis of the findings of new studies, the committee concludes that the evidence of an association between mixed solvent exposure and scleroderma is limited/suggestive and that some evidence points toward TCE exposure in particular. This constitutes a change in IOM's 2003 conclusion.

Amyotrophic Lateral Sclerosis

IOM 2003 Conclusions

IOM (2003) considered four case-control studies in evaluating the association between solvent exposure and amyotrophic lateral sclerosis (ALS) (Chio et al. 1991; Gunnarsson et al. 1992; Strickland et al. 1996; McGuire et al. 1997). Chio et al. defined exposure by using occupational information drawn from hospital charts and municipal records. Gunnarsson et al. and Strickland et al. used only self-reported exposure. Only McGuire et al. (1997) used a more sophisticated assessment of exposure by a panel of industrial hygienists. In that study, the age- and education-adjusted OR for self-reported exposure to solvents in both men and women was 1.6 (95% CI, 1.1-2.5). However, when the industrial-hygiene assessment was used, the association was attenuated (OR, 1.2; 95% CI, 0.8-1.9). Of 28 specific agents assessed, only "cleaning solvents or degreasers" had a positive association with both self-reported exposure (OR, 1.8; 95% CI, 1.2-2.8) and industrial-hygiene assessment (OR, 1.9; 95%: CI 1.1-3.3). The association was limited to females in stratified models, and there was no evidence of a dose-response relationship. On the basis of the results of that study and the insufficiency of exposure assessment in the other studies, IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to solvents and ALS.

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2008 Evaluation

No new studies of exposure to solvents and ALS 2003 were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to solvents and ALS.

Parkinson Disease

IOM 2003 Conclusions

IOM (2003) evaluated studies with only Parkinson disease as the outcome measure rather than the more generic diagnosis of parkinsonism. Only two studies were found to be sufficiently rigorous in design to be useful in providing evidence on the relationship between solvent exposure and Parkinson disease (Hertzman et al. 1994; Seidler et al. 1996). Both were case-control studies that used prevalent cases, and one of the studies (Hertzman et al. 1994) focused on pesticides and presented little pertaining to solvent exposure. Although both studies found an association between past exposure to solvents and Parkinson disease, they were likely to have been subject to recall bias. Overall, little attention has been focused on solvent exposure as a risk factor for Parkinson disease. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents reviewed and Parkinson disease.

2008 Evaluation

The relationship between exposure to solvents and Parkinson disease was assessed in a case-control study in the United Kingdom that was restricted to men (McDonnell et al. 2003). Potential cases (176) were obtained by searching the pension-fund archive of a major engineering company for death certificates that mentioned Parkinson disease, and potential controls (599) were identified from the same database. Exposure to solvents was determined on the basis of occupational records, which were not available for many subjects. In the end, 57 people with the diagnosis (32% of the 176) and 206 controls (34% of the 599) were included in the analysis. Thirty-one people with the disease and 93 controls had worked in jobs involving exposure to solvents; the OR was 1.53 (95% CI, 0.81-2.87). There was a significant trend in the odds of disease with increasing duration of exposure. The study included a small number of cases and lacked information on other possible risk factors or confounders.

Another case-control study of Parkinson disease assessed the role of solvent exposure (Dick et al. 2007). It was conducted in five European countries and included 767 prevalent cases and 1,989 controls. Cases were ascertained through clinical visits or by reviewing medical records, and the control group included a mixture of hospital controls and community controls. Subjects were interviewed about lifetime occupational and hobby-related exposure to solvents. The OR was 1.01 (95% CI, 0.84-1.23) for any exposure to solvents. When average annual intensity of exposure was evaluated, the ORs for those with low and high exposure were 1.17 (95% CI, 0.92-1.50) and 0.88 (95% CI, 0.69-1.12), respectively. This study is characterized by a large number of subjects and provided no evidence of an association between solvent exposure and Parkinson disease.

A study by Gash et al. (2008) included a group of 30 workers at a single factory who had long-term (8-33 years) chronic exposure to TCE. The study was initiated because one of the workers had received a diagnosis of Parkinson disease and suspected that his occupational exposure to TCE was a factor in his disease. The investigators mailed questionnaires to 134 former workers, of whom 65 responded and 27 agreed to a clinical examination. Three workers with workstations adjacent to the TCE source and subjected to chronic inhalation and dermal exposure from the handling of TCE-soaked metal parts had Parkinson disease, whereas workers more distant from the TCE source and receiving chronic respiratory expo-

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sure displayed features of parkinsonism. Because of the "cluster investigation" type of design, the significance of the study is difficult to judge.

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and Parkinson disease.

Multiple Sclerosis

IOM 2003 Conclusions

At the time of the IOM (2003) report, four case-control studies of solvent exposure (in general) and multiple sclerosis (MS) had been conducted in Scandinavia. Two had negative results, and the other two, conducted in Sweden and based on overlapping populations, reported some positive associations between self-reported occupational and leisure-time solvent exposure and MS in men. The positive findings are tempered by the limited quality of exposure assessment, the lack of adjustment for potential confounders, and small sample and were thus short of "limited/suggestive" evidence of an association. No studies focused specifically on TCE or PCE were found. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and MS.

2008 Evaluation

No additional studies of solvent exposure and MS were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and MS.

Alzheimer Disease

IOM 2003 Conclusions

After evaluating five studies of solvent exposure and Alzheimer disease, all of which were case-control studies, IOM (2003) concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and the disease. 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. Several authors commented that occupational solvent exposure is most likely to occur in men, but population-based studies suggest that women are at greater risk for Alzheimer disease.

2008 Evaluation

The committee identified a study that was not included in the 2003 IOM review (Tyas et al. 2001). It evaluated the relationship between solvent exposure and Alzheimer disease in a prospective cohort. Cognitively intact subjects completed a questionnaire that assessed many potential risk factors, including exposure to solvents. Five years later, 36 subjects developed the disease, and 694 remained cognitively intact. The analysis for exposure to solvents (degreasers), which included 28 cases and 531 noncases, resulted in an OR of 0.88 (95% CI, 0.31-2.50). Although the study had a unique design, it does not have a major effect on the overall evidence to determine whether an association exists between solvent exposure and Alzheimer disease.

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- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and Alzheimer disease.

Neurobehavioral Effects

IOM 2003 Conclusions

Review of over 300 studies of solvent exposure and neurobehavioral symptoms (such as fatigue, lack of coordination, and sensory disturbances) or neurobehavioral test results (such as results of tests of attention, reaction time, and visuomotor coordination) by IOM (2003) yielded only seven studies that had isolated former exposure from current exposure. The only way to identify chronic effects that continue past the period of active exposure is through studies that consider formerly (but not currently) solvent-exposed people. Of those studies, several (Mikkelsen et al. 1988; Parkinson et al. 1990; Hanninen et al. 1991; Daniell et al. 1993; Lundberg et al. 1995; Stollery 1996) found evidence of continued deficits in formerly solvent-exposed workers compared with reasonably constituted unexposed groups. Many studies compared painters or other solvent-exposed workers with people in similar occupations (such as carpentry) that did not have the same exposure history. The most specific and sophisticated evaluation of those previously exposed to solvents was conducted by Daniell et al. (1999), who found dose-dependent effects on neurobehavioral function some time after cessation of exposure. Although each of the studies found that one or more symptoms or test realms showed a deficit in function, there is not much consistency among the studies in which specific symptom or test was found to be affected, the comparison groups are not necessarily precisely comparable, and confounding factors were controlled to various degrees, so even relatively consistent evidence of some effects falls short of conclusive data. IOM concluded that there is limited/suggestive evidence of an association between past exposure to solvents and neurobehavioral outcomes, with the most support for decrements in visuomotor and motor function, for fatigue, for headache, and for difficulty in concentrating.

2008 Evaluation

Recent studies have addressed the relationship between solvent exposure and neurobehavioral outcomes, including one focused on TCE (Reif et al. 2003) and one on PCE (Janulewicz et al. 2008). The study by Reif et al. (2003) evaluated neurobehavioral function in 184 adults who had been exposed through contaminated drinking water many years before testing. Higher exposure was associated with poorer performance on several tests (such as digit symbol and contrast sensitivity) and with increased symptoms (such as confusion, depression, and tension). The study of PCE (Janulewicz et al. 2008) addressed prenatal exposure in the Cape Cod water-contamination episode and evaluated school records for indications of learning or behavioral disorders. It found essentially no support of such an association. The studies of community water-supply contamination continue to provide mixed findings, as was found in the 2003 IOM report.

- The committee concludes that there continues to be limited/suggestive evidence of an association between past solvent exposure and neurobehavioral outcomes.

Long-Term Reduction in Color Discrimination

IOM 2003 Conclusions

IOM (2003) reviewed a series of studies of occupational solvent exposure that addressed an ill-defined combination of past and present solvent exposure in relation to measures of color discrimination.

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Because the exposure was continuing, it is not possible from these studies, a number of which provide evidence of a relationship between solvent exposure and reduction in color discrimination, to address the question of whether there is a long-term effect that continues beyond the period of exposure. One report addressed dry-cleaning workers exposed to PCE (Gobba et al. 1998) and found that there was a dose-related decrement in visual discrimination that did not decline after a period of diminishing exposure but, as in other studies, there was no exposure-free interval before visual testing, so the study results do not address whether PCE's effects were short-term or long-term. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and long-term reduction in color discrimination.

2008 Evaluation

A report by Schreiber et al. (2002) that was not included in the IOM review evaluated residents who lived in an apartment building or attended day care above a dry-cleaning facility. Changes in visual contrast sensitivity and visual acuity were addressed but not color discrimination itself. The authors reported that visual contrast sensitivity but not visual acuity was reduced. No additional reports on reduction in color discrimination were identified.

- The committee concludes that there continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to TCE or PCE and long-term reduction in color discrimination.

Long-Term Hearing Loss

IOM 2003 Conclusions

IOM (2003) reviewed a series of studies addressing the potential for occupational solvent exposure to exacerbate the well-established adverse effect of noise exposure on hearing. Several of the studies that were reviewed yielded evidence that supported the hypothesis that workers exposed to solvents and noise would experience greater hearing loss than those exposed to noise alone (Bergström and Nyström 1986; Morata et al. 1993, 1997), but none considered whether there is a long-term effect of solvents that continues beyond the period of exposure, and there is some evidence that the effect is a short-term one. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents and long-term hearing loss.

2008 Evaluation

No additional studies of solvent exposure and long-term hearing loss were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents and long-term hearing loss.

Long-Term Reduction in Olfactory Function

IOM 2003 Conclusions

Several cross-sectional studies addressed occupational solvent exposure and reduction in olfactory function. Studies of paint manufacturing were mixed—one positive (Schwartz et al. 1990) and the other negative (Sandmark et al. 1989)—and the one study of toluene exposure reported a positive associa-

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tion (Hotz et al. 1992). In all cases, exposure was current, and no study could evaluate whether any adverse effects persisted beyond the period of exposure. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents and long-term reduction in olfactory function.

2008 Evaluation

No additional studies of solvent exposure and long-term reduction in olfactory function were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents and long-term reduction in olfactory function.

CONCLUSIONS

The committee undertook a general review of the epidemiologic evidence on TCE, PCE, and solvent mixtures. On the basis of the reviews referred to in this chapter, the committee concludes that the strongest evidence of an association between TCE or PCE and health outcomes is in the category of *limited/suggestive evidence of an association* related to the following end points:

- Esophageal cancer (PCE)
- Lung cancer (PCE)
- Breast cancer (PCE)
- Bladder cancer (PCE)
- Kidney cancer (TCE, PCE)
- Miscarriage (PCE)

The strongest evidence of an association between solvent mixtures and health outcomes is in the category of *limited/suggestive evidence of an association* related to the following end points:

- Adult leukemia
- Multiple myeloma
- Kidney toxicity
- Liver toxicity (hepatic steatosis)
- Female infertility
- Scleroderma
- Neurobehavioral effects

For all other outcomes considered, the committee categorized the evidence as *inadequate/insufficient* for determining whether associations exit.

Chapter 6 presents a more detailed review of the epidemiologic studies that involved community exposure to drinking water contaminated with TCE or PCE, and Chapter 8 reviews studies of former Camp Lejeune residents. Chapter 7 provides an integrated discussion of the epidemiologic evidence in context with the toxicologic evidence on TCE and PCE.

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6

Epidemiologic Studies of Solvent-Contaminated Water Supplies

The results of studies of human populations that were exposed to solvents through water supplies were included as part of the comprehensive evaluations of the epidemiologic literature provided in Chapter 5. In those evaluations, the epidemiologic literature was considered comprehensively to evaluate a global question: What is the evidence that a particular chemical may be associated with a specific health outcome? The studies were dominated by occupational studies of dry cleaners and other workers, which typically have greater exposures that are well documented but are restricted to populations of relatively healthy men and involve exposure pathways that differ from those at Camp Lejeune.

This chapter focuses more on studies that addressed situations that approximate the circumstances at Camp Lejeune more closely (see Table 6-1). Those situations involve episodes of solvent contamination of water used by a community's population for drinking, bathing, and other purposes. As at Camp Lejeune, a population's water supply was contaminated with solvents from industrial sources, distributed to the public, and used for household purposes. Thus, such studies have had to grapple with the same methodologic challenges that face investigators of the Camp Lejeune situation, including exposure assessment, population identification, potential confounding factors, and small study size and statistical power. The exposed populations typically include the full spectrum of people—all ages, both sexes, and varied health status (including pregnancy)—with varied behavior related to water use and widely varying background influences on disease risk.

An examination of those studies in more detail contributes to the context and strategy for addressing environmental health concerns at Camp Lejeune. First, there may be methodologic lessons to be learned, such as beneficial research strategies that would be suitable for application to epidemiologic studies of Camp Lejeune. Second, as noted above, the studies share some important characteristics with the Camp Lejeune situation. Thus, in setting priorities for outcomes warranting attention at Camp Lejeune, the committee considered the studies of contaminated community water supplies as a distinctively relevant group of epidemiologic studies. Unfortunately, as noted below, methodologic limitations limited the contribution of such studies despite their advantages in being somewhat analogous to the Camp Lejeune water-contamination situation.

METHODS

Study Designs

The contamination events whose study is in Table 6-1 came to attention in a variety of ways. In one instance, a disease cluster raised attention (Mallin 1990), but it appears that all the others came to notice because environmental contamination raised concern about potential health effects among exposed

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TABLE 6-1 Summary of Epidemiologic Studies Involving Drinking-Water Contamination with TCE, PCE, and Other Solvents

Exposure Source	Study Design	Primary Exposure Assessment	Health Outcomes Evaluated	Relative Risk (95% CI); n = exposed cases	Potential Confounders Considered	Reference and Comments
Tucson, AZ (well contamination, 1969-1981)						
TCE, dichloroethylene and chromium in groundwater from dumping of military, industrial wastes	Case-control	Parental residence or employment in census tracts likely to receive contaminated water at least 1 month before and during first trimester of pregnancy[a]	Congenital heart defects	1969-1987: relative OR estimated to be 3 times greater in exposed group; n = 246 1969-1981: Bove et al. (2002) reanalyzed data to restrict analysis to contamination period; prevalence ratio, 2.6 (2.0-3.4)		Goldberg et al. 1990, Bove et al. 2002; used inappropriate controls; imprecise geographic delineation of contaminated area
	Ecologic	Maternal address at delivery linked by GIS to census tracts served by contaminated wells, identified with groundwater transport and fate model	Low birth weight, very low birth weight, term low birth weight	1979-1981 (years with computerized records): very low birth weight (n = 13): adj OR, 3.3 (0.5-20.6)	Gestational time, prenatal-care index, pregnancy complications, pregnancy illness, congenital abnormalities, sex of baby, race of baby, Hispanic origin of baby, parity, age of mother, mother's education, marital status	Rodenbeck et al. 2000
San Bernardino County, CA (well contamination, 1980-1990; study period, 1988-1998)						
TCE, ammonium perchlorate in groundwater (unspecified source)	Ecologic	Residential location (13 census tracts served by contaminated wells)[a]	16 cancer types	Significantly higher number of cases than expected for uterine cancer (n = 124): RR, 1.4 (99% CI, 1.1-1.7); melanoma (n = 137): RR, 1.4 (99% CI, 1.1-1.8)		Morgan and Cassady 2002; authors attribute excess uterine cancer, melanoma to higher SES of exposed population[b]
Santa Clara, CA (well contamination, 1980-1981; study period, 1980-1985)						
Trichloroethane in groundwater contaminated by underground waste-solvent storage tank at semiconductor plant	Cohort	Maternal residence in census tract served by contaminated well[a]	Spontaneous abortion, congenital abnormalities, low birth weight	Spontaneous abortion (n = 64): adj RR, 2.3 (1.3-4.2); congenital malformations (n = 10): RR, 3.1 (1.1-10.4); no low-birth-weight babies born in contaminated area	Maternal age; alcohol consumption, smoking, prior fetal loss, number previous pregnancies, ethnicity, maternal exposure to organic solvents, petrochemicals, pesticides, x rays	Deane et al. 1989

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	Cohort	Residential proximity to contaminated well, defined by census tracts, period[a] For 1981, groundwater fate and transport model coupled to water-distribution model to estimate maternal first-month, first-trimester exposures	Spontaneous abortion, congenital abnormalities, low birth weight	Original study area: spontaneous abortion (n = 89): RR, 3.5 (1.2-10.3); congenital malformations (n = 96): RR, 4.3 (1.2-14.7); low birth weight (n = 281): RR, 0.7 (0.2-1.8) Adjacent census tract likely to have been exposed to water from contaminated wells: spontaneous abortion (n = 86): RR, 0.3 (0,1-1.1); congenital malformations (n = 105): RR, 0.9 (0,1-6.6); low birth weight (n = 294): RR, 1.7 (0.5-6.0)		Wrensch et al. 1990
	Case-control	Consumption of tap, bottled water during first trimester (mostly tap water vs mostly bottled water); among women consuming mostly tap water, source (groundwater vs surface water) by county	Adverse pregnancy outcomes	Telephone respondents: spontaneous abortion: OR, 2.2 (1.4, 3.6); anomalies: OR, 1.8 (95% CI: 0.8, 4.1) Mail respondents: spontaneous abortion: OR, 1.3 (0.8, 2.0); anomalies: OR, 0.8 (0.4, 1.7)		Hertz-Picciotto et al. 1992; (unadjusted) ORs are for consumption of tap, bottled water; hazard ratios also reported for spontaneous abortion by county (San Mateo, Alameda, Santa Clara), source of water (ground vs surface) in women consuming mostly tap water
	Case-control	Maternal address at delivery linked to areas in (exposed), outside (unexposed) distribution system[a]	Congenital cardiac abnormalities	1981-1982: RR, 2.2 (1.2-4.0), n = 12 1981-1983: adj RR, 1.5 (0.8-3.0), n = 143	Mother's education, race	Swan et al. 1989 Shaw et al. 1990
Denver, CO						
TCE, PCE contamination of municipal wells from hazardous-waste sites	Cohort	Hydraulic simulation model, GIS used to assign mean TCE levels based on residential (census block) location	Neurobehavioral effects	Higher exposure (>15 µg/L; n = 20) associated with poorer performance on digit-symbol test ($P = 0.07$), contrast-sensitivity tests C, D ($P = 0.06, 0.07$); 37-83% higher mean scores for confusion, depression, tension; strong interaction with alcohol consumption	Self-reported consumption of seafood once a week or more, years of education, smoking, alcohol consumption	Reif et al. 2003

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TABLE 6-1 Continued

Exposure Source	Study Design	Primary Exposure Assessment	Health Outcomes Evaluated	Relative Risk (95% CI); n = exposed cases	Potential Confounders Considered	Reference and Comments
Denver, CO						
TCE, PCE contamination of municipal wells from hazardous-waste sites	Cohort	Hydraulic simulation model, GIS used to assign mean TCE levels based on residential (census block) location	Neurobehavioral effects	Higher exposure (>15 µg/L; n = 20) associated with poorer performance on digit-symbol test (P = 0.07), contrast-sensitivity tests C, D (P = 0.06, 0.07); 37-83% higher mean scores for confusion, depression, tension; strong interaction with alcohol consumption	Self-reported consumption of seafood once a week or more, years of education, smoking, alcohol consumption	Reif et al. 2003
Northwestern Illinois						
Groundwater contamination (organic chemicals, heavy metals) due to dumping of solid, liquid wastes	Ecologic	Residence by county, ZIP code in nine-county area[a]	Bladder cancer	RR in males (n = 21), 1.7 (1.1-2.6); females (n = 10), 2.6 (1.2-4.7)		Mallin 1990
Woburn, MA, 1964-1983						
TCE, PCE in municipal wells contaminated by industrial wastes	Cohort	Annual estimates of fraction of water supply served by contaminated wells; residential history[a]	Childhood leukemia, adverse pregnancy outcomes, childhood disorders	Positive associations reported for childhood leukemia (n = 20; P = 0.001), eye or ear anomalies (n = 9; P < 0.0001), CNS or chromosomal or oral cleft anomalies (n = 8; P = 0.01), kidney or urinary tract disorders (n = 43; P = 0.02), lung or respiratory disorders (n = 192; P = 0.05), perinatal deaths, 1970-1982 (n = 4; P = 0.003)	Smoking, age, prior fetal loss, prior perinatal death, prior low birth weight, prior musculoskeletal anomaly, SES, year pregnancy ended	Lagakos et al. 1986
	Case-control	Average, cumulative exposure metrics[a]	Childhood leukemia	RR, 8.3 (0.7-94.7); n = 19; dose-response trend (P < 0.05)		Costas et al. 2002
Cape Cod, MA						
Leaching of PCE from inner vinyl lining of asbestos cement water-distribution pipes	Case-control	Residential history, water flow, pipe characteristics to predict PCE in distribution system[a]	Leukemia and lung, breast, colorectal, bladder, kidney, pancreatic, brain, liver cancer	Cancers with increased risk: leukemia (no latency): adj OR, 2.1 (0.9-5.2); n = 34	Sex, age at diagnosis or index year, vital status, education level, occupational exposure to solvents, prior medical treatment with irradiation	Aschengrau et al. 1993

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Case-control	See Aschengrau et al. (1993)	Breast cancer	Adj OR (for latency of 0-15 years), 1.6 (1.1-2.4) to 1.9 (1.1-3.2); n = 930	Age at diagnosis or index year, vital status, family history of breast cancer, age at first live birth or stillbirth, prior breast cancer or benign breast disease, occupational exposure to solvents	Aschengrau et al. 1998, 2003 (combined data presented)[c]
Case-control	Annual PCE levels (see Aschengrau et al. [1993]) coupled to information on tap water consumption and bathing habits	Breast cancer	Adj OR (for latency of 0-15 years), 1.4 (0.8-2.5) to 1.9 (0.6-5.9); n = 154[d]	Age at diagnosis or index year, family history of breast cancer, prior breast cancer, age at first live birth or stillbirth, occupational exposure to PCE	Vieira et al. 2005
Case-control	See Aschengrau et al. (1993)	Colorectal, lung, brain, pancreatic cancer	Cancers with increased risk: colorectal cancer (11-year latency): adj OR, 1.7 (0.8-3.8); n = 311	Age at diagnosis or index year, vital status, sex, occupational exposure to solvents, history of polyps, inflammatory bowel disease, or ulcerative colitis, occupational history associated with colorectal cancer (exposure to asbestos, solvents)	Paulu et al. 1999
Cohort	Residential history; leaching, transport model; water-distribution model, GIS to predict monthly levels at nodes in distribution system	Birth weight, gestation duration	No associations found between exposure and birth weight or gestational duration; n = 1,353	Gestational age, maternal race, education level, history of low-birth-weight child, occupational exposure to solvents, use of self-service dry cleaning, residential proximity to dry-cleaning establishments, prior preterm delivery, obstetrical complications in current pregnancy	Aschengrau et al. 2008
Upper New Jersey (Bergen, Essex, Morris, Passaic Counties)					
TCE, PCE	Ecologic	Residential location[e]	Leukemia	Leukemia, males: SIR, 1.0 (0.7-1.5), n = 25; females: SIR, = 1.5 (1.0-2.2), n = 28	Fagliano et al. 1990

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TABLE 6-1 Continued

Exposure Source	Study Design	Primary Exposure Assessment	Health Outcomes Evaluated	Relative Risk (95% CI); n = exposed cases	Potential Confounders Considered	Reference and Comments
TCE, PCE	Ecologic	Average 1984-85 levels from quarterly monitoring data for 75 towns	Leukemia, NHL	For highest exposure stratum: leukemia in males: RR, 1.1 (0.8-1.4), n = 63; females: RR, 1.4 (1.1-1.9), n = 56; acute lymphocytic leukemia in females <20 years old: RR, 3.3 (1.3-8.2), n = 6; NHL in males: RR, 1.2 (0.9-1.5), n = 78; females: RR, 1.4 (1.1-1.7), n = 87; diffuse large-cell NHL in males: 1.6 (1.0-2.4), n = 26; females: RR, 1.7 (1.1-2.6), n = 24; non-Burkitt's in males: RR, 1.9 (0.5-6.8), n = 3; females: RR, 3.2 (1.2-8.2), n = 6		Cohn et al. 1994
TCE, PCE from landfill leachate, industrial waste disposal, leaking underground storage tanks	Case-control	Maternal address at delivery; monthly estimates from quarterly monitoring data from 75 municipalities[a]	SGA, preterm birth, birth weight, birth defects, fetal death	TCE: CNS defects: OR, 1.7 (90% CI, 0.8-3.5), n = 6; neural-tube defects: OR, 2.5 (90% CI, 0.9-6.4), n = 4; oral-cleft defects: OR, 2.2 (90% CI, 1.2-4.2), n = 9 PCE: oral-cleft defects: OR, 3.5 (90% CI, 1.3-8.8), n = 4	Maternal age, race, education level, primipara, prior fetal loss or stillbirth, sex of child, adequacy of prenatal care	Bove et al. 1995; if adjusted OR differed by more than 15%, adjusted value was reported as OR; no distinction made between adjusted and unadjusted values
Southern Finland						
TCE, PCE from industrial sources, dump site	Ecologic	Residence at diagnosis (Hausjarvi and Hattula)[a]	Liver cancer, NHL, Hodgkin disease, multiple myeloma, leukemia	Increaseded risks in Hausjarvi: leukemia: RR, 1.2 (0.8-1.7), n = 33; Hattula: NHL: RR, 1.4 (1.0-2.0), n = 31; Hodgkin disease: RR, 1.4 (0.7-2.5), n = 11		Vartiainen et al. 1993
Taoyuan County, Taiwan						
Hazardous-waste site (formerly electronics factory)	Case-control	Residential proximity to contaminated wells, period of death[a]	Cancers	Leading causes of cancer deaths in all male population: liver: adj MOR, 2.6 (1.2-5.5), n = 53; stomach: adj MOR, 2.2 (1.0-4.9), n = 39; lung: adj MOR, 1.8 (0.8-3.9), n = 41; colorectal: adj MOR, 0.8 (0.2-2.9), n = 26; all: adj, MOR, 2.1 (1.3-3.3), n = 266		Lee et al. 2003

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Indiana, Illinois, Michigan						
Superfund sites	Cohort	Listed in TCE exposure registry[a]	Multiple health outcomes	Statistically significant results for stroke: adj OR, 3.2 (1.1-9.0) to 4.1 (1.5-11) for max. TCE quartiles, n = 60; respiratory allergies: adj OR, 2.2 (1.1-4.2), n = NR; asthma, emphysema: adj OR, 1.8 (1.0-3.3) for cumulative exposure, n = NR	Age, sex, smoking, occupational exposure, education level for stroke; age, sex for asthma, emphysema	Burg and Gist 1999
Michigan, Indiana, Pennsylvania, Arizona						
Superfund sites	Cohort	Listed in TCE exposure registry[a]	Multiple health outcomes	Excess cases over lifetime of registry for anemia, other blood disorders, liver problems, rashes, eczema, other skin allergies		Davis et al. 2005
Iowa						
Water-disinfection byproducts	Ecologic	Water-supply source	Bladder, breast, colon, lung, prostatic, rectal cancer	No associations between TCE or PCE and cancers		Isacson et al. 1985

[a]See Table 6-2 for more detailed exposure data.
[b]Higher than average SES predicts access to health care, which enhances detection of melanoma. Access to health care also makes it more likely that postmenopausal women will receive estrogen-replacement therapy, which is linked to increased endometrial cancer (main form of uterine cancer).
[c]Adjusted OR in Aschengrau et al. (1998) ranged from 0.6 (0.0-3.7) to 2.3 (0.6-8.8), n = 258; adjusted OR in Aschengrau et al. (2003) ranged from 1.5 (1.0-2.4) to 1.9 (1.0-3.5) for 0-15 years of latency, n = 672.
[d]Analysis restricted to nonproxy subjects.
Abbreviations: CI = confidence interval, CNS = central nervous system, GIS = geographic information system, MOR = mortality odds ratio, NHL = non-Hodgkin lymphoma, NR = not reported, OR = odds ratio, PCE = perchloroethylene, RR = relative risk, SES = socioeconomic status, SGA = small for gestational age, SIR = standardized incidence ratio, SRR = standardized rate ratio, TCE = trichloroethylene.

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residents. All the studies included a broad enough geographic area or period to contrast disease risks in people with greater and smaller degrees of exposure associated with the contamination, and the quality of the exposure assessment varied widely among the studies. A time element was also used to define exposure, such as residence in a specific location over a specific calendar period. In some instances, people were asked detailed questions to help to characterize exposure beyond the geography and the period of contamination related to water use. Because exposure was driven largely by residential location, the studies are susceptible to confounding by the many geographically based attributes that affect disease other than the exposure of interest, such as socioeconomic differences or associated lifestyle factors, for example, tobacco or alcohol use and quality of medical care that might affect diagnoses. Some studies (Hertz-Picciotto et al. 1992; Aschengrau et al. 1993, 1998; Costas et al. 2002; Reif et al. 2003) included individual interviews, which made it possible to assess and consider a variety of potential confounders in the analysis.

Exposure Assessment

Table 6-2 presents exposure data from the studies in Table 6-1 that monitored concentrations of trichloroethylene (TCE), perchloroethylene (PCE), and other solvents in production wells from which water was pumped for delivery to the distribution systems of the affected communities. The way in which the episodes studied were identified (the discovery of contaminated water supplies at some time) means that monitoring data on a water supply for the putative agents were largely nonexistent except for periods close to or right after identification of the problem, as was the case at Camp Lejeune. In Woburn, Massachusetts, for example, concerns about possible contamination from industrial wastes in the late 1970s led to the testing and closing of wells in which increased concentrations of TCE (267 ppb) and PCE (21 ppb) were detected (Lagakos et al. 1986). The Santa Clara County contamination incident in California is another example of a well's being shut down immediately after the detection of high concentrations of trichloroethane (1,700 ppb) (Deane et al. 1989). Another well-known contamination episode occurred in Cape Cod, Massachusetts, as a result of leaching of PCE from the vinyl lining of asbestos-cement water-distribution pipes. The lining of the pipes had been applied in the late 1960s, but the contamination was discovered only after sampling was carried out more than 10 years later. In that instance, the range of the measurements collected throughout the distribution system constituted evidence of spatial variability in contaminant concentrations: concentrations at low-use locations (1,600-7,750 μg/L) were 20-5,000 times higher than those at high-use locations (1.5-80 μg/L).

To compensate for the lack of monitoring data in studies of increased health risks associated with contaminated drinking water, investigators used exposure assessments whose complexity depended on the sources of data and the metrics. One of the simplest surrogates of exposure relied on residential proximity to the source of contamination. In those cases, exposure was inferred from residence in areas served by contaminated wells (Deane et al. 1989; Swan et al. 1989; Goldberg et al. 1990; Wrensch et al. 1990; Lee et al. 2003); in one study, the inference was aided by groundwater transport and fate models to define potentially exposed areas (Rodenbeck et al. 2000) and in another by groundwater sampling (albeit later than the study period) to verify the classification of exposed areas downstream of the source (hazardous-waste site) of the contamination (Lee et al. 2003). In the only study that relied on biologic monitoring to evaluate potential solvent exposure, Vartiainen et al. (1993) compared urinary metabolites of TCE and PCE (dichloroacetic acid and trichloroacetic acid) in residents of municipalities with and without groundwater contamination.

More sophisticated exposure-assessment approaches have used hydraulic modeling of the water-distribution system that accounts for the pumping of water from both contaminated and uncontaminated wells and for characteristics of the pipe network (such as geometry, age, diameter, and leaks). For example, several studies of the potentially affected community in Woburn, Massachusetts, used a hydraulic mixing model to estimate the fraction of water received by each residence weekly (Lagakos et al. 1986) or monthly (MDPH/CDC/MHRI 1996; Costas et al. 2002) from contaminated wells. Wrensch et al. (1990)

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TABLE 6-2 Summary of Reported Water-Monitoring Data in Published Epidemiologic Studies[a]

Source of Contamination	Sampling Period	Sampling Location	Contaminant	Concentrations	Reference and Comment
Tucson Valley, AZ					
Industrial wastes	1981	9 public wells	TCE	6-239 ppb	Goldberg et al. 1990
San Bernardino County, CA					
Unspecified	1980 and later 2001	20 public wells	TCE	0.09-97 ppb (<5 ppb in distribution system since 1991)	Morgan and Cassady 2002
		Public wells (number not specified)	Ammonium perchlorate	5-98 ppb (<18 ppb since 2001)	
Santa Clara County, CA					
Underground waste-solvent storage tank (near semiconductor plant)	Dec. 7, 1981	Public well 13	1,1,1-TCA	1,700 ppb	Deane et al. 1989; Swan et al. 1989; Wrensch et al. 1990; well 13 removed from service on Dec. 7, 1981
	Dec. 14, 1981		1,1,1-TCA	8,800 ppb	
	Mar. 1982		1,1,1-DCE	8.8 ppb	
	Mar. 1982	Public well 8	TCA	33.5 ppb	
			DCE	9.6 ppb	
Northwestern Illinois					
Dumping of solid, liquid wastes	1982-1988	Public well 1	Benzene	<1 ppb	Mallin 1990
			1,2-Dichloroethane	1.6-2.1 ppb	
			1,1,1-TCA	7 ppb	
			1,1-Dichloroethane	2-11 ppb	
			trans-1,2-DCE	8-42 ppb	
			Methylene chloride	<1 ppb	
			PCE	<1ppb	
			TCE	2-10 ppb	
			Chloroform	1.3 ppb	
			Dibromochloromethane	<1 ppb	
		Public well 2	Benzene	1.3-2 ppb	
			1,2-Dichloroethane	1.7-2 ppb	
			1,1,1-TCA	1 ppb	
			1,1-Dichloroethane	1-4.6 ppb	
			trans-1,2-DCE	14-38 ppb	
			Methylene chloride	1-5 ppb	

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TABLE 6-2 Continued

Source of Contamination	Sampling Period	Sampling Location	Contaminant	Concentrations	Reference and Comment
			PCE	5.1 ppb	
			TCE	2-15 ppb	
			Chloroform	27 ppb	
			Dibromochloromethane	12 ppb	
Woburn, MA					
Industrial wastes	1979	Public wellsG and H	TCE	267 ppb	Lagakos et al. 1986; Costas et al. 2002; Byers et al. 1988; wells closed after sampling in May 1979
			PCE	21 ppb	
			Trichlorofluoroethane	23 ppb	
			DCE	28 ppb	
			Arsenic	0.0020 ppm	
			Chloroform	11.8 ppb	
Cape Cod, MA					
TCE in inner vinyl lining of asbestos-cement water-distribution pipes	~1980	Water-distribution pipes Low-use sites Medium- and high-use sites	PCE	1,600-7,750 µg/L 1.5-80 µg/L High value of 18,000 µg/L at dead-end sites in Falmouth reported in Paulu et al. (1999)	Aschengrau et al. 1993, 1998, 2003, 2008; Paulu et al. 1999; Massachusetts Department of Environmental Protection began program of flushing, continuous bleeding in 1980 to lower PCE concentrations
Rhode Island	1976	Water-distribution systems	PCE	800-2,000 µg/L	Paulu et al. 1999
Upper New Jersey (Bergen, Essex, Morris, Passaic Counties)					
Landfill leachate; industrial waste disposal, leaking underground storage tanks	1985-1988	49 distribution systems serving 75 towns		Monthly estimates:	Bove et al. 1995
			TCE	55 ppb	
			PCE	26 ppb	
			1,1,1-TCA	18 ppb	
			Carbon tetrachloride	7 ppb	
			1,2-Dichloroethane	19 ppb	
			Total DCE	16 ppb	
			Benzene	2 ppb	
			Total trihalomethanes	299 ppb	

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	1984-1985	Routine sampling in distribution systems of 27 towns in Lower Passaic River and Saddle River drainage basin	14 unspecified compounds	Sum of average of nontrihalomethane VOCs (no. towns) 72 µg/L (1) 67 µg/L (1) 47 µg/L (1) 40 µg/L (1) 37 µg/L (1) 12 µg/L (1) 9 µg/L (1) 7 µg/L (1) 5 µg/L (4) 3 µg/L (2) 2 µg/L (2) 1 µg/L (9) 0 µg/L (2)	Fagliano et al. (1990)
Southern Finland					
Industrial sources (Oitti)	1992	Drinking-water samples	TCE, PCE (Oitti)	100-200 µg/L	Vartiainen et al. 1993
Dump site (Hattula)	July 1992		TCE (Hattula)	212 µg/L 66 µg/L	
Taoyuan County, Taiwan					
Hazardous-waste site (formerly electronics factory)	Oct. 1999-May 2000	Residential wells		Median (range)	Lee et al. 2003; previous reports of off-site groundwater contamination indicated up to 930 and 4,800 µg/L for TCE and PCE, respectively
			Vinyl chloride	0.003 µg/L (ND-72.3)	
			Tetrachloroethene	2.95 µg/L (ND-5,228.3)	
			TCE	28.43 µg/L (ND-1,790.7)	
			1,1-DCE	1.35 µg/L (ND-1,240.4)	
			1,1,1-TCA	0.67 µg/L (ND-1,504.4)	
			cis-1,2-DCE	3.05 µg/L (ND-1,376.0)	
			1,1-Dichloroethane	1.81 µg/L (ND-227.9)	
Indiana, Illinois, Michigan					
National Priorities List sites		TCE subregistry site	TCE	Maximum/median (no. household samples)	Burg and Gist 1999
		Verona Well Field and Dowaglac (MI)		2,000/6.0 ppb (66)	
		McGraw-Edison Corporation (MI)		733/1.0 ppb	
		Superior Street (IN)		19,380/84.0 ppb (134)	
		Central Area (IN)		114/0.4 ppb (28)	
		Gemeinhardt Piccolo Company (IN)		1,600/4.0 ppb (100)	

(Continued)

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TABLE 6-2 Continued

Source of Contamination	Sampling Period	Sampling Location	Contaminant	Concentrations	Reference and Comment
		Conrail Rail Yard (IN)		1,520/78.0 ppb (49)	
		Acme Solvents Reclamation, Inc. (IL)		100/1 ppb (13)	
		Beloit Corporation (IL)		3/2 ppb (3)	
		Byron Johnson Salvage Yard (IL)		249/9.1 ppb (25)	
		Frinks Industrial Waste (IL)		16/14.0 ppb (5)	
		Southeast Rockford groundwater contamination (IL)		122/15.0 ppb (331)	
		Warner Electronic Brake and Clutch Company (IL)		5,220/234.0 ppb (74)	
Michigan, Indiana, Illinois, Pennsylvania, Arizona					
National Priorities List sites (n = 15)		Residential sites	TCE	Median concentrations, 0.4-234 ppb; maximum concentrations, 3-24,000 ppb	Davis et al. 2005
Iowa					
		Sampling of drinking water from treatment plants at municipalities in Iowa serving 1,000 or more residents	TCE PCE 1,2-Dichloroethane 1,1,1-TCA	Data reported as % of towns with detectable VOC concentrations by source of supply water (surface, <46 m, 46-152 m, >152 m)	Isacson et al. 1985

[a]Following studies were also evaluated for water-monitoring data, but none were found: Cohn et al. (1994); Hertz-Picciotto et al. (1992); Reif et al. (2003); Rodenbeck et al. (2000); Shaw et al. (1990); Viera et al. (2005).

Abbreviations: DCE = dichloroethylene, ND = not detected, PCE = perchloroethylene, TCA = trichloroacetic acid, TCE = trichloroethylene, VOC = volatile organic compound.

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developed a groundwater fate and transport model to estimate concentrations of trichloroethane in the aquifer that supplied water to the production well (in which the contamination was detected); the results were coupled to a water-distribution model to estimate the probability that water from the contaminated well reached specific locations in the distribution system. In studies carried out to investigate the cancer risk posed by PCE-contaminated drinking water in Cape Cod, Massachusetts, investigators used a water-distribution model (the Webler-Brown model) that predicted the amount of PCE leaching from the vinyl-lined pipes and then transported to residences served by the distribution systems (Aschengrau et al. 1993, 1998; Paulu et al. 1999); the modeling effort was later improved on by using geographic information systems (GISs) (rather than tax-assessor maps) to geocode key elements of the water-distribution system and study participants' residences (Aschengrau et al. 2003). Reif et al. (2003) also took advantage of the capabilities of GISs and linked residences of persons living near the Rocky Mountain Arsenal whose water supply had been contaminated with TCE to results from a hydraulic model (EPANET) to reconstruct 1985 contaminant concentrations at specific nodes in the distribution system.

Cognizant that exposure is influenced not only by concentrations of a contaminant in drinking water but by the amount of water consumed or used in other ways, investigators have also gathered individual-level information about consumption patterns, bathing and showering habits, and other water-related behavior with questionnaires or interviews. The resulting data have been used to form the primary exposure measure for evaluating the associations between contaminated drinking water and adverse health outcomes (for example, consumption of cold tap water by source and year) (Shaw et al. 1990) and have been incorporated as covariates in the multiple logistic regression models that have been applied. For example, in addition to evaluating the effect of living in an area served by a contaminated well in Santa Clara, California, consumption of cold tap water at home (Deane et al. 1989; Wrensch et al. 1990) and water-filter use (Wrensch et al. 1990) were assessed. To evaluate heterogeneity in the effects of contaminated water on cancer risk due to water-related behavior, stratified analyses by usual bathing habits (mostly showers, mostly baths, or about equal baths and showers) were conducted in the studies carried out in the Upper Cape region of Massachusetts (Ashengrau et al. 1993, 1998; Paulu et al. 1999). It would be of interest to examine results of studies that used more and less sophisticated approaches to assess exposure, but the contamination episodes are so different from one another that it is impossible to isolate the quality of exposure assessment as an independent influence on the final results.

Health-Outcome Assessment

With few exceptions (such as the study of neurobehavioral function in a Colorado population exposed to solvents [Reif et al. 2003] and the study of pregnancy outcome in Santa Clara, California [Hertz-Picciotto et al. 1992]), all the studies have assessed health outcomes on the basis of existing records. Much of the attention in those studies has been on birth outcomes, including the information obtainable through birth records, which constitute one of the few universal health registry systems available in the United States and eliminate concerns about nonresponse. For all geographic areas and for all periods going back several decades, birth weight, duration of gestation, and selected social and demographic factors can be ascertained. Thus, a number of studies addressed birth weight, preterm birth, and stillbirth.

Some areas have population-based registries of congenital defects and cancer that provide comprehensive coverage of geographically defined populations and periods and allow evaluation of associations with exposures also defined by geography and time. Studies of cancer in Massachusetts, Illinois, and New Jersey have relied on outcome ascertainment from population-based registries (Fagliano et al. 1990; Burg and Gist 1999; Aschengrau et al. 2003). The advantage of using established birth or disease registries is efficiency in time and expense of the studies, but they are limited by the quality of the registries (with respect to comprehensiveness and accuracy of diagnoses) and constrain the scope of studies to the subset of health outcomes on which data are available. Pregnancy outcomes and cancer are often important concerns in episodes of solvent-contaminated water, but they are rarely the only concerns, and other outcomes remain unaddressed.

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The alternative approach, applied in Colorado (Reif et al. 2003) and California (Deane et al. 1989; Hertz-Picciotto et al. 1992) is to identify the population of concern on the basis of exposure (a product of location and time), sample that population to include the desired exposure contrasts, and conduct more detailed health assessments of individuals. Reif et al. (2003) selected residentially exposed persons and tested neurobehavioral characteristics, outcomes not otherwise assessable with existing registries. Similarly, miscarriage assessment requires collecting information directly from potentially affected people, as was done in Santa Clara, California. There is a marked increase in the expense, but the approach allows a focus on the health outcomes of greatest concern rather than those on which data are readily available. In contrast, the need to rely on respondent cooperation to identify people and include them in a study incurs a cost in the potential for bias due to nonparticipation, which is not a problem with registry-based studies. The quality of self-reported data may also be lower for some outcomes.

RESULTS

The studies of populations exposed to contaminated water supplies have generated a wide array of positive associations, as reflected in Table 6-1. Among the most increased relative risks were those for congenital heart defects (odds ratio [OR], 2.6; 95% confidence interval [CI], 2.0-3.4) in Tucson, Arizona (Bove et al. 2002); spontaneous abortion (OR, 2.3; 95% CI, 1.3-4.2) and congenital defects (OR, 3.1; 95% CI, 1.1-10.4) in Santa Clara, California (Deane et al. 1989); and liver cancer (OR, 2.6; 95% CI, 1.2-5.5) in Taoyuan County, Taiwan (Lee et al. 2003).

Although the evidence linking solvents in water supplies to individual outcomes seems impressive in specific studies, the lack of corroboration among studies (or even attempted corroboration in many instances) weakens their credibility. Furthermore, these largely opportunistic studies typically considered the full array of available outcomes from birth certificates, registries, and other available sources and reported the positive findings that emerged from such broad explorations. The universe of other outcomes considered in the studies is not always clear, and the broader universe of investigations of water-contamination episodes that did not identify "interesting" associations and were therefore never published is also unknown and could be substantial. In addition, the focus in many cases on rare outcomes (such as individual birth defects and childhood cancers) renders the resulting risk estimates highly imprecise and driven by as few as two or three cases. Although it is possible that some of the scattered, isolated findings are meaningful and could eventually be proved to indicate a replicable association with a specific health outcome, the results presented in Table 6-1 do not support such a conclusion. Therefore, even acknowledging that the studies are more directly comparable with the Camp Lejeune circumstances than the methodologically stronger studies discussed in Chapter 5, the committee concluded that the epidemiologic literature would be most effectively used if all of it, rather than only studies of community water-contamination episodes, were comprehensively evaluated. The studies reviewed in this chapter were given extra attention because of their applicability, and in some instances (such as the evidence linking water solvents to breast cancer on Cape Cod [Aschengrau et al. 1998, 2003]) the findings contributed substantially to identifying priorities. However, our interpretation of the epidemiologic studies in their totality was not dominated by them.

DISCUSSION

The studies discussed in this chapter yielded reports that were deemed by the investigators and scientific journals to be worthy of publication and that might have generated a disproportionate representation of positive findings. The findings of those studies should not be viewed as a representative or comprehensive set of findings, because investigation of contamination episodes is commonly undertaken by health departments but rarely reported in the literature. Relative to studies of occupational cohorts, which often have much higher and better documented exposures and large populations, the community studies

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are limited by the quality of exposure data and to various extents by the low size of their populations, particularly if such rare outcomes as childhood leukemia and congenital defects are being addressed. Even if the different routes of exposure—inhalation vs ingestion—are recognized, the occupational studies tend to dominate the evidence. The committee has incorporated the information from solvent water-contamination studies, as warranted, into the overall assessments of the epidemiologic evidence as reflected in the tables and categorization of evidence in Chapter 5 and focuses here on any special contributions as a function of the more direct relevance of water contamination as the source of exposure.

With regard to methods, the studies in this chapter have largely started with the conventional approach of characterizing a broad geographic area and period and relating health outcomes to estimated exposure. However, several have gone further in refining the exposure estimates by using sophisticated engineering models (particularly in Woburn, Massachusetts) in ways that are broadly applicable to the situation at Camp Lejeune. Similarly, the Cape Cod studies have gone beyond routinely available information on water source to estimate delivered dose.

The strategy pursued by Reif et al. (2003) and in the series of Santa Clara, California, studies (for example, Wrensch et al. 1990) also warrants consideration. They began with an episode of environmental contamination but proceeded to conduct individual data collection with interviews, medical records, and, in the case of the Denver, Colorado, episode, direct evaluation of potentially affected individuals. Available records have merit as a starting point, but for many health outcomes of interest it is essential to go further to collect new data.

CONCLUSIONS

Collectively, the epidemiologic studies of solvent contamination of water supplies and adverse health effects are of limited quality. If their distinctive strengths and limitations are taken into account, such studies contribute to the overall assessment of the epidemiologic literature, but the committee has judged that their strengths (comparability with Camp Lejeune in exposure pathways and diversity of exposed population) do not overcome their limitations (especially quality of exposure assessment, lower range of exposure, and imprecision in measures of association) to allow identification of high-priority outcomes on the basis of their results alone.

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7

Integration of Findings from the Toxicologic and Epidemiologic Literature

The charge to the committee was to review the scientific evidence concerning associations between exposure to contaminated water and adverse health effects applicable to the population at Camp Lejeune. To address the general evidence on health effects of trichloroethylene (TCE) and perchloroethylene (PCE), the committee reviewed the toxicologic literature (see Chapters 3 and 4) and the epidemiologic literature (see Chapters 5 and 6) for a comprehensive array of health outcomes, drawing on recent authoritative reviews where feasible and appropriate. This chapter considers those sets of literature together to identify health outcomes that are most plausibly due to TCE and PCE, focusing on health outcomes on which the lines of evidence converge.

In evaluating the potential for toxic effects in humans from a chemical exposure, data from human studies are usually considered the most relevant. However, human data are often limited by the size of the population(s) studied, the information on actual exposure concentrations, and other confounding factors. Thus, data from toxicologic studies are also used to evaluate the potential for various health effects from exposure to chemicals under more controlled conditions and usually at higher exposure concentrations than in the human population. The strength of the toxicologic data is dependent on the size, number, and types of studies conducted, as well as replication of study designs and results. The relevance of the animal data to humans is dependent on those factors as well as a number of toxicokinetic and dynamic factors, and they must be weighed carefully in evaluating the potential for environmental exposures to cause various health effects in humans.

In the following sections, the human and animal toxicologic data are discussed briefly for those health outcomes for which some information was available from both types of evidence. In some cases, the human data weighed more heavily because of the strength of the data and/or the association with the exposure. In other cases, the animal data weighed more heavily because of greater integrity of the data or more in-depth evaluation of the dose-response relationship and mechanisms involved.

CANCER OUTCOMES

Chapter 5 reviewed the epidemiologic studies and concluded that there was limited/suggestive evidence of an association between chronic exposure to TCE or PCE and cancers of the breast, bladder, kidneys, esophagus, and lungs. Toxicologic studies did not report significantly increased cancers of the breast, bladder, or esophagus, and rodent lung cancers were judged not to be relevant to humans because of known species differences in metabolism and organ sensitivity. Thus, for outcomes having limited/suggestive epidemiologic evidence of an association, positive concordance with the toxicologic evidence was strongest for kidney cancer. Studies of TCE and PCE found increases in kidney cancer in rats treated chronically at high doses. The mechanism by which the solvents exert their effects on the

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kidneys appears to be similar in rats and humans, and this strengthens the plausibility that these solvents caused kidney cancer in the occupational studies that found suggestive evidence of associations.

Toxicologic studies have reported findings of liver cancer, lung cancer, male reproductive cancers, and mononuclear-cell leukemia in mice or rats exposed to high concentrations of TCE or PCE, but species differences in metabolism and response indicate that these cancers are not relevant to humans (see more detailed discussion in Chapter 4). The epidemiologic evidence on these cancers (except lung cancer) was judged to be inadequate/insufficient to determine whether associations exist.

NONCANCER OUTCOMES

Hepatic Toxicity

Animal toxicity studies indicate that high concentrations of TCE and PCE are required to induce hepatocellular injury (cell replication, peroxisome proliferation, DNA adducts, and increase in serum enzymes released from damaged cells). Mice have a greater capacity to oxidize these solvents than humans. The epidemiologic evidence also shows clear effects of acute, high-level exposure to TCE and other solvents on the liver, but there is little evidence of persistent effects of chronic low-level exposure. The strongest evidence in the epidemiologic literature is limited/suggestive evidence of an association between chronic exposure to solvents and hepatic steatosis.

Renal Toxicity

TCE and PCE have some nephrotoxic potential in rodents and humans. Animal toxicity studies indicate that high concentrations of TCE and PCE are required to induce nephrotoxicity, such as injury to the proximal tubules, glomerulonephropathy, and karyomegaly. Chronic injury to cells of the proximal tubule is considered a prerequisite for the development of kidney cancer caused by TCE. The metabolism and mode of nephrotoxic action of TCE and PCE appear to be similar, although PCE and its metabolites appear to be more potent. Renal effects are due primarily to metabolites formed via the glutathione conjugation pathway. This metabolic pathway is similar qualitatively, but not quantitatively, in rats and humans. Humans have been shown to have a lower capacity than rats to convert TCE and PCE to reactive derivatives of glutathione conjugates. Epidemiologic studies of the effects of short-term and long-term solvent exposure on renal function have yielded limited/suggestive evidence of an association between high levels of solvent exposure, but not chronic low-level exposure, and acute tubular necrosis. A series of case-control studies of chronic glomerulonephritis in relation to solvent exposure have generated mixed evidence regarding an association; several reasonably strong positive studies showed dose-response gradients.

Reproductive Outcomes

The committee found independent toxicologic and epidemiologic evidence of associations between exposure to solvents and reproductive outcomes, but there was limited convergence for specific reproductive end points. For example, toxicologic studies have reported adverse effects on indicators of male fertility in rats and mice after high-dose exposure to TCE and PCE, respectively. Findings in human studies were not sufficiently consistent to support any firm conclusions, but a few studies showed a potential association with male infertility. With regard to female fertility, the epidemiologic evidence suggested an association between solvents in general and reduced fecundability (the ability to become pregnant), but there was little evidence in the toxicology literature to support female infertility, even after exposure at high concentrations.

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The human evidence of an association between chronic exposure to TCE or PCE and congenital malformations was judged to be inadequate to support conclusions. However, the toxicologic data provide strong evidence that neither solvent is associated with congenital malformations in rats. Adverse pregnancy outcomes (other than congenital malformations) were not seen in toxicologic studies of maternal exposure to TCE in rats, but reduced fetal weight in rats was seen in studies of maternal exposure to PCE. Data on female rats exposed before mating and during pregnancy indicate reduced offspring survival at high concentrations. Studies of mating pairs of rats or mice exposed during mating and throughout one or more pregnancies also showed reduced numbers of litters and increased perinatal mortality. Epidemiologic evidence provides some indication that solvent exposure during but not before pregnancy is associated with miscarriage but not with preterm birth or reduced birth weight, and there is no direct evidence on perinatal mortality. Although specific parallels between reduced litter size and perinatal mortality in rodent models and increased miscarriage in humans should not be drawn, the data suggest some corroboration of adverse reproductive effects of exposure during gestation. Pregnancy outcomes in rats after high maternal inhalation exposure to PCE indicate a reduction in intrauterine growth. Epidemiologic studies have addressed fetal growth after exposure to solvents in general and have not found sufficient evidence of an adverse effect. Only a few toxicologic studies of pregnancy outcomes after exposure of males before mating are available, and they indicate a reduction in number of litters at high inhalation concentrations. The epidemiologic evidence on paternal exposure to TCE and adverse pregnancy outcomes was inadequate/insufficient to support any conclusions.

Neurologic Effects

Epidemiologic studies of solvent exposure and neurobehavioral outcomes have for the most part addressed nonspecific solvents or solvents in the aggregate. Overall, there is limited/suggestive evidence of an association between principally inhalation exposure to solvents and neurobehavioral outcomes; the most support is of visuomotor and motor function, fatigue, headache, and deficits in concentration. Most of those effects were reported concurrently with exposure, and there has been little study of whether effects persist after exposure ceases. Animal toxicologic studies also report effects on the nervous system, such as depression of the central nervous system, attention deficits, deficits in visual discrimination, alterations in visual evoked potentials, altered sleep pattern, and reduced exploratory behavior in rats and rabbits exposed for weeks to moderate vapor concentrations of TCE. These changes generally appear to be reversible. Residual auditory loss resulting from losses of cochlear spiral ganglion and hair cells have been observed in rats inhaling high concentrations of TCE. Similar effects have been found in rodents exposed to PCE. In addition, studies of PCE have shown changes in behavior and neurochemical markers at lower levels. Some animal data suggest sensitive windows during development when organisms are more susceptible to PCE exposure, which results in alterations of neurologic development and behavior.

Immunologic Outcomes

Epidemiologic studies have provided some support of two immunologically mediated end points: chronic glomerulonephritis and scleroderma. There is limited/suggestive evidence of an association between mixed solvent exposure and both end points and some indication of a specific association between TCE and scleroderma. The toxicologic data provide strong evidence that TCE can act as a skin sensitizer, modulate existing asthma, produce immunosuppression, and influence autoimmune diseases. Data on PCE have only a suggestion of effects on allergic sensitization and immunosuppression.

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CONCLUSIONS

The committee did not find sufficient evidence to justify causal inference for any health effects it reviewed. However, some effects were identified from a review of the collective evidence from epidemiologic and toxicologic investigations as being relevant health outcomes to consider in future studies of exposures at Camp Lejeune, including kidney cancer, renal toxicity, hepatic toxicity, neurotoxicity, and autoimmune disease. Although other health end points with less support from the existing literature should not be excluded from consideration, such findings are more likely to reflect random error if not supported by additional contexts in the literature.

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8

Studies of the Camp Lejeune Population

This chapter summarizes research that directly addresses the potential impact of contaminated water supplies on the health of Camp Lejeune residents. Although there is indirect evidence on the chemicals of concern from laboratory research and epidemiologic studies of other populations (Chapters 4-7), such information must be extrapolated to the Camp Lejeune setting and population, and extrapolation carries the potential for incorrect inferences. To the extent that scientifically valid epidemiologic research has been conducted directly on Camp Lejeune residents, extrapolation is unnecessary. Thus far, the research on the Camp Lejeune population has been limited with respect to the scope of health outcomes considered and the quality of exposure assessment.

COMPLETED STUDIES

The Agency for Toxic Substances and Disease Registry (ATSDR) is the only agency to have performed epidemiologic studies of the Camp Lejeune population exposed to water supplies contaminated with volatile organic compounds (VOCs). In a public health assessment, ATSDR (1997a) judged that exposure to VOCs in drinking water did not pose health risks to adults but raised questions about risks to children who may have been exposed via their mothers while in utero. Thus, the first study was a case-control study of pregnancy outcomes. Two published analyses resulted from that effort: ATSDR (1998), which focused on trichloroethylene (TCE) and perchloroethylene (PCE) exposures at Tarawa Terrace; and Sonnenfeld et al. (2001), which considered only PCE exposure at Tarawa Terrace. Both analyses focused on pregnancy outcomes regarding live-born infants, including mean birth weight, small for gestational age (SGA), and preterm delivery. ATSDR initially planned to evaluate fetal deaths, also, but that plan was abandoned because of the small number (83) of fetal deaths identified with the computerized state database and because the cause of fetal death was missing from death certificates in most cases (ATSDR 1998). The study methods used in the two analyses will be presented here first, followed by the results of each.

Outcome Measures

Birth weight and pregnancy duration were derived from North Carolina birth records. Preterm birth was defined as a live birth occurring before completion of 37 weeks of gestation. SGA, defined as below the 10th percentile of weight for gestational age, was calculated by using published sex-specific growth curves for white newborns in California (Williams et al. 1982) because a standard birth-weight distribution for the military population was not available. According to Sonnenfeld et al. (2001), of the three standards considered for use, the California standard was the one that fit best when all races were included.

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The study considered a base population of 12,493 singleton live births delivered after at least 20 weeks gestation to women residing in base housing during the period 1968-1985 who were identified through birth records (ATSDR 1998). That population did not include births to mothers who resided on the base during pregnancy but were no longer residents of Onslow County at the time of delivery. Residential mobility may be substantial: according to ATSDR, "approximately one-third of the women who sought prenatal care at the Navy Regional Medical Center at Camp Lejeune moved or were transferred before they delivered" (ATSDR 1998, p. 16). Although exposures were presumed to have occurred before 1968, a starting date of January 1, 1968, was chosen because electronic files of North Carolina birth certificates began that year. The analyses assumed delivery of contaminated water via the water-distribution system through February 1985 (ATSDR 1998; Sonnenfeld et al. 2001).

ATSDR documented that 523 (4%) of the 12,493 live births were excluded because exposure to contaminated water supplies was for less than 1 week or exclusively before conception (44), or because data were missing, inconsistent, or insufficient (479), leaving 11,970 live births for the mean-birth-weight analyses. Of the11,970 live births, 6,117 (51%) were to women who resided at Tarawa Terrace at the time of birth, 31 (0.26%) were to women who resided at Hospital Point (which received water from Hadnot Point), 141 (1.2%) were to women who resided in housing units temporarily supplied by Hadnot Point during a fuel-pump failure, and 5,681 (47%) were to women who resided in housing supplied by the Holcomb Boulevard system, were considered to be unexposed, and served as a comparison group. Additional exclusions were made for the SGA analyses (eight births with gestational age under 22 weeks) and the preterm-birth analyses (the eight births excluded from the SGA analyses plus 101 births classified as implausibly heavy preterm births).

Exposure and Confounder Data

Exposure was defined by linking birth records to the base's family housing records according to the mother's address at delivery and the father's name. The housing records, which contained dates of residence, were used to estimate the dates when the mother resided in base housing units. The study "assumed that each family resided in only one base housing unit during pregnancy" (ATSDR 1998, p. 21). A residential-history substudy indicated that about 55% of mothers in the study moved during their pregnancies, and 3.5% of them moved between base housing units (ATSDR 1998).

The 1998 ATSDR study included all identified births regardless of exposure, whereas the 2001 Sonnenfeld et al. study limited the exposed population to residents of Tarawa Terrace. The Tarawa Terrace residents were considered exposed to PCE from water contaminated by an off-base dry-cleaning establishment (ABC One-Hour Cleaners). ATSDR's analysis also included births to two groups of residents who were exposed to TCE and other VOCs through the Hadnot Point water system on either a long-term or a transitory basis. Transitory exposure (called short-term in the ATSDR report) covered all births to residents who received drinking water from the Holcomb Boulevard water system and who were pregnant for at least 1 week of the 12-day period during January-February 1985 when Hadnot Point water served the Holcomb Boulevard system. In both studies, residents of the base trailer park were excluded because housing records were incomplete, and, as noted above, a few births to mothers residing on base for a very short time or during ambiguous exposure periods were excluded. The remaining births to mothers residing on the base were considered unexposed, including births to all residents of the Marine Corps Air Station, Rifle Range, and Courthouse Bay and the remaining residents of Berkeley Manor, Midway Park, Paradise Point, and Watkins Village.

Exposure was categorized further by length of residence as a proxy for duration of exposure. Duration of exposure was defined as length of time before the birth that the mother lived at the residence specified on the birth certificate. Because inclusion in the study was based on maternal residence at the time of birth, exposure duration was relative to the end of pregnancy. Duration-of-exposure analyses excluded births that occurred after exposure ended in 1985. In analyses, duration of exposure was categorized as never, 1-3 weeks, 4-10 weeks, 11-20 weeks, over 20 weeks and less than the entire pregnancy,

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the entire pregnancy and less than 1 year before the last menstrual period, and the entire pregnancy and at least 1 year before the last menstrual period.

The covariates available for analysis were limited to information that could be obtained from the birth certificates and military records. They included infant's sex, year of birth, and gestational age; maternal age, race, parity, education level, military pay grade, adequacy of prenatal care, marital status, and history of fetal death; and paternal age, education level, and military pay grade. Gestational age was calculated from the date of the last menstrual period reported on the birth certificate. Women with records showing a month and year of last menstrual period but missing information on the day had their day interpolated to 15. Women with records missing the month of the last menstrual period were excluded. In the remaining data, there was evidence of gestational-age misclassification in that 17% of preterm infants of gestational age less than 28 weeks had birth weight above the 90th percentile of the distribution for the standard population (ATSDR 1998). Preterm infants above the 90th percentile for birth weight at 36 weeks of gestation were excluded from the preterm-delivery analysis but not the birth-weight or SGA analysis.

Results of the Sonnenfeld et al. Study

Exposure was not equally distributed across various demographic groups. Exposed women were less likely to be white, less likely to live in officers' housing, less likely to be college-educated, and less likely to have a college-educated partner (Sonnenfeld et al. 2001). Those differences raise questions about whether any observed differences in reproductive outcomes by exposure status were confounded by sociodemographic factors because not all the variables were examined as potential confounders or included in the adjusted analyses that were reported.

The overall results of the study indicated that "long-term" PCE exposure from the Tarawa Terrace water system was not strongly associated with reduced birth weight, preterm birth, or SGA. The mean birth weight in the PCE-exposed group was 26 g less than that in the PCE-unexposed group (90% confidence interval [CI], -43 to -9) (note use of 90% CI rather than 95% CI). The unadjusted odds ratio (OR) for PCE exposure and preterm birth was 1.0 (90% CI, 0.9-1.1) and for PCE exposure and SGA 1.2 (90% CI, 1.0-1.3). It was noted that adjustment for potential confounders had little effect on the results. The authors reported no consistent patterns in the associations between PCE exposure and mean birth weight, preterm birth, or SGA by duration of exposure.

In subgroup analyses, Sonnenfeld et al. reported that long-term exposure to PCE from the Tarawa Terrace water system was marginally associated with lower mean birth weight and an increase in risk of SGA but only in newborns of mothers more than 35 years old and mothers who had already had more than two fetal losses. The birth-weight analysis was adjusted for mother's age, history of fetal loss, race, and residence in officers' housing and infant's gestational age, year of birth, and sex. The SGA analysis was adjusted for mother's age, history of fetal loss, parity, residence in officers' housing, and education and infant's year of birth. The authors noted that older PCE-exposed mothers were different from their unexposed counterparts in race, college education of husbands, and household income (defined by the father's rank). However, not all those variables were included in the analyses. Specific subgroups showed statistically significant effects, but no formal hypothesis test for the presence of interaction between subgroups defined by maternal age or history of fetal loss was mentioned.

The authors concluded that there was no association between PCE exposure and mean birth weight or preterm birth and that there was a weak association between PCE exposure and SGA in all groups. In subgroup analyses, they observed stronger associations between PCE exposure and low birth weight and SGA of infants of mothers who had a history of fetal death and mothers more than 35 years old.

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Results of the Agency for Toxic Substances and Disease Registry Study

This section focuses on aspects of the ATSDR results that are distinctive from the Sonnenfeld et al. results. ATSDR reported analyses of PCE exposure at Tarawa Terrace that were unadjusted, and this may have contributed to the slight differences from Sonnenfeld et al. in birth-weight results (-24 g; 90% CI, -41 to -7), but the SGA and preterm delivery results were identical. In spite of the reported difference, the birth-weight results were said to show no association, because the magnitude of the difference was viewed as clinically negligible. The duration-of-exposure analyses were identical, but the effect-modification results were slightly different because of different exclusion of data and more limited control for confounding. In particular, the OR for PCE exposure and SGA in women more than 34 years old was 4.0 (90% CI, 1.6-10.2) after adjustment only for officers' housing. No exposure-response patterns were observed for PCE exposure and mean birth weight or SGA in women who had had fetal deaths.

The much smaller population of TCE-exposed births was analyzed with stratification by residence. Births in the long-term TCE-exposed group were to mothers living in housing ordinarily served by the Hadnot Point water-distribution system. Overall, there was limited evidence of a reduction in mean birth weight (reduction by 108 g; 90% CI, -230 to 13) or of increased risk of SGA (OR, 1.5; 90% CI, 0.5-3.8), interpreted by ATSDR as modest associations. The reported results were unadjusted despite differences between the two groups in the distribution of infant sex; mother's age, pay grade, history of fetal death, and parity; and father's education. Few analyses of interaction were conducted because of the small sample. TCE effects were found to be modified by infant sex for both birth weight and SGA. The study reported an increased risk of SGA in TCE-exposed male infants (OR, 3.9; 90% CI, 1.1-11.9) on the basis of three exposed cases. According to a rate estimated from the female control group, one exposed SGA female infant was expected; none was observed. No risk of any of the outcomes was found in the temporarily exposed population with a maximum exposure duration of 12 days.

Review and Evaluation

Retrospective case-control studies can be extremely difficult to conduct when historical information on exposure, outcome, and covariates—challenges applicable to the study of birth outcomes at Camp Lejeune—is scarce. This section discusses limitations in identifying the study population, assignment of exposure, confounder control, and analytic approach.

Exposure misclassification is a major limitation of the ATSDR and Sonnenfeld et al. analyses. A number of exposed births were misclassified as unexposed because of incorrect assumptions about the water-delivery system, which ATSDR later identified. Both studies assumed that all mothers who resided in family housing in the Holcomb Boulevard system service area from 1968 through 1984 were unexposed. In the course of exposure reconstruction of the Tarawa Terrace system, it was learned that the Holcomb Boulevard plant came on line in June 1972 and that before then the housing now served by Holcomb Boulevard was served by the Hadnot Point water-supply system. Thus, any mothers who resided in family housing in the Holcomb Boulevard system service area in 1968-1972 were actually exposed. That is an important (and correctible) source of misclassification that has the potential to alter study results dramatically because a sizable number of pregnancies will be reclassified from unexposed to exposed.

Other limitations in exposure classification in these studies are more difficult to correct. Aspects of residential-history assignment would have caused exposure misclassification of unknown magnitude. First, all mothers were assumed to have had only one residence on the base and to have been unexposed at all other residences. The residence-history validation study estimated that a sizable proportion of mothers changed housing on the base during their pregnancies. Second, the contaminant exposure and its variation over time are impossible to quantify accurately. As reviewed in Chapter 2, water-supply measurements of contaminant concentrations are sparse, and the data were collected only in the 1980s. Third, there is no information about individual behaviors that affect exposure (such as water consumption and frequency

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and duration of bathing and showering). Fourth, exposure was determined exclusively by place of *residence*, excluding workplace and other locations in which exposure may have occurred.

The studies relied on North Carolina birth-certificate data from Onslow County linked to base housing records. That was a feasible and efficient approach to conducting a study, but the information-retrieval process and restricted data sources have implications for population selection, outcome definition and quality, and confounder control. In particular, the base population used in the studies does not represent the entire population of live births to all women who resided at Camp Lejeune in 1968-1985. Infants whose mothers were transferred or moved away from Camp Lejeune before giving birth were not included. In addition, because residence at birth determined inclusion, all exposure-duration analyses were relative to the end of pregnancy. For instance, nearly all infants who were exposed only during the first trimester were excluded. Beyond its obvious impact on interpretation of the exposure-duration analyses, the effect of a selection approach based on location at the time of delivery is unknown.

Outcome variables were based on information included on birth certificates, and there are known limitations in the quality of some items (Wingate et al. 2007). In particular, accurate estimates of the date of the last menstrual period are critical for defining SGA and preterm birth. The ATSDR study found a disproportionate number of heavy liveborn infants relative to a standard population of the same gestational age—a reminder of the fallibility of birth-certificate-based gestational-age estimates. Outcome-based exclusions varied among the three outcomes; preterm birth outcome was related to the largest number of exclusions.

Control for confounding is another challenge. Because of reliance on birth-certificate data on the period of the exposure episode, such key confounders as maternal smoking and alcohol use were not available. In addition, in reported analyses, control for confounding was not often done even for variables that were available. The ATSDR report gives unadjusted estimates of the primary results even though the exposed and unexposed populations differed in important respects and the study protocol (ATSDR 1994) stated that all analyses would be adjusted for race. The sensitivity of results to potential confounders should be examined more thoroughly.

The implications of the results of subgroup analyses are unclear. The interactions of exposure with maternal age, history of fetal loss, and infant sex do not appear to be based on strong assumptions but instead resulted from exploratory statistical analysis. Although such interactions cannot be discounted, they should not be taken as evidence of an important effect of exposure. But these results are often cited as the primary study findings (for example, ATSDR 2005a). It is well known that overinterpretation of subgroup analyses can be misleading; such analyses typically suffer from low power and higher than nominal probability of reporting false positive effects (for example, Stallones 1987; Brookes et al. 2004; Weiss 2008). In addition, the various subgroup analyses used different numbers of observations and different adjustment variables, depending on the report, outcome, and exposure variable. Subgroup membership should be described, and the sensitivity of results to data exclusions and more thorough confounder adjustment should be examined.

CURRENT STUDIES

Study Methods

ATSDR's 1997 public-health assessment for Camp Lejeune led to a recommendation that an epidemiologic study be performed to evaluate whether mothers exposed to chlorinated solvents in drinking water, particularly TCE and PCE, during pregnancy have a higher risk of giving birth to a child with a birth defect or cancer, given the recognition of the limited scientific information on how those chemicals might affect a fetus or child (ATSDR 1997a). (ATSDR withdrew this report on April 28, 2009.) ATSDR later began a multistep process to determine the appropriateness of such a study. First, the childhood health problems to study were identified. On the basis of its review of the scientific literature, ATSDR decided to focus on specific childhood cancers and birth defects: childhood leukemia, childhood non-Hodgkin lymphoma, spina bifida, anencephaly, cleft lip, and cleft palate (ATSDR 2005a). The rationale

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for focusing on those particular outcomes given the prior epidemiologic and toxicologic research and considerations of feasibility (specifically, statistical power) is discussed later in this chapter.

The second step was to identify the children eligible for the study by conducting a telephone survey. The survey, conducted from September 1999 to January 2002, built on the database initially constructed for the two case-control studies of preterm birth and fetal growth (ATSDR 1998; Sonnenfeld et al. 2001). The survey sought information on all children who were born in 1968-1985 to mothers who resided on the base at any time during their pregnancies. Births in Onslow County were included, as were births that occurred after mothers were transferred off the base. ATSDR attempted to locate and contact the parents of each eligible child to elicit information on the child's health, to confirm that the mother was a Camp Lejuene resident during the pregnancy, and to collect data on potential confounders. It identified eligible children in multiple ways. Initially, it used the birth-certificate information from the previous Camp Lejeune study of SGA (ATSDR 1998) that included only women who were residents on the base at the time of their deliveries. Next, children born in 1968-1985 to mothers whose pregnancies occurred while they lived in base housing but who delivered after moving off the base were identified by word of mouth (for example, in parent groups), by referrals from other parents during their interviews, or by public requests (via the mass media, e-mails from the Marine Corps, and notices) that parents contact ATSDR. ATSDR surveyed the parents of 12,598 eligible children of an estimated 16,000-17,000 eligible births, representing an overall participation rate of 74-79%, depending on the estimated number of births that occurred off the base (ATSDR 2003). Parents were asked if their children had had birth defects or childhood cancer. A total of 106 cases that fit the case definition of parent-reported birth defect or childhood cancer were reported in the survey: 35 neural-tube defects, 42 oral clefts, and 29 childhood cancers.

The third step was to confirm the children's health problems by reviewing their medical records. As of June 23, 2008 (Bove and Ruckart 2008), of the 35 reported or potential cases of neural-tube defects, 15 were confirmed (six anencephaly and nine spina bifida), 13 were ruled out, two had no medical records for confirmation, three were ineligible, and the parents of two potential cases refused to participate. For children who had parent-reported oral clefts without medical records, a dental examination was used to confirm that surgery was performed as a result of a cleft lip or palate. Of the 42 children who were reported to have oral clefts, 24 were confirmed (11 cleft palate and 13 cleft lip with or without cleft palate), 11 were ruled out, four had no medical records for confirmation and dental examinations could not confirm the conditions, and the parents of three potential cases refused to participate. Of the 29 reported childhood leukemia or non-Hodgkin lymphoma cases, 13 were confirmed (11 leukemia and two non-Hodgkin lymphoma), eight were ruled out, one had no medical records for confirmation, four were ineligible, and the parents of three potential cases refused to participate. The parents of 15 children with neural-tube defects, 23 children with oral clefts, and 13 children with leukemia or non-Hodgkin lymphoma were successfully interviewed.

The fourth and final step of the process is to conduct a case-control analysis that incorporates water-system modeling; that work is under way. The primary hypotheses concern the association between drinking TCE- or PCE-contaminated water during the first trimester and specific birth defects and the association between drinking TCE- or PCE-contaminated water during pregnancy and childhood cancers. The hypotheses are extended to incorporate contaminant concentration and personal exposure (taking into account the amount of water consumed by the mother or used in showering, hand-washing dishes, and so on).

The base population for the case-control study consists of all live births to mothers residing at Camp Lejuene in 1968-1985 who participated in the survey. Cases are confirmed birth defects (diagnosed by the age of 5 years) or childhood cancers (diagnosed by the age of 20 years). (Planned sensitivity analyses will also include unconfirmed cases.) Controls will be randomly selected from all other births included in the survey to attain a target of 10 controls for each case.

Exposure assessment will be based on the ATSDR water-distribution system modeling (see Chapter 2). That includes a protocol for modeling the present water-distribution system and then developing historical distribution-system models for the study period and generating estimates of contaminant concentrations in the water supply by year and housing complex. The stated exposure variables will be "ex-

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posure status, concentration level, and/or percent of water from a contaminated source during the specific time periods of interest in the 1-year period before the child's birth. TCE and PCE will be evaluated separately" (ATSDR 2005a, p. 29). Categorization of exposure is planned to be collapsed into ever vs never and into more refined exposure categories. Cut points will be determined from the contaminant-concentration distributions. Water use and consumption will be incorporated into the exposure metrics.

According to the ATSDR protocol (ATSDR 2005a, page 25), with alpha set at 0.10, 80% power, and an exposure prevalence of 40%, minimum detectable ORs are as follows: 4.3 for 15 cases and 2.9 for 28 cases of neural-tube defects, 3.6 for 20 cases and 2.5 for 36 cases of oral cleft, and 5.2 for 14 and 4.3 for 19 cases of childhood cancer. Even with the uncertainty about the total number of cases that will eventually be included in the analysis and even under the more optimistic scenario, statistical power is low.

Review and Evaluation

Owing to the paucity of measurements of PCE and TCE concentrations in contaminated water at Camp Lejeune during the period of interest, exposure assessment is a major limitation of the current birth-defect and childhood-cancer study. ATSDR has proposed to use water-system modeling as a way to improve the quantification of exposure. As indicated in Chapter 2, exposure estimates based on water-system modeling require a number of assumptions, and the validity of many of the assumptions is impossible to evaluate in light of the historical measurement data. Given the lack of information on which wells were used to supply water on any particular day, the quality of exposure estimates based on water-system modeling is highly uncertain, especially for the quantification of PCE and TCE concentrations over the short periods of interest for the study of birth defects. In addition, historical information about water behavior will be available in two pregnancy-related periods (the mother's questionnaire asks about only two periods: before and during the first trimester and during the second and third trimesters), and that information will be obtained only if the mother can be interviewed. Recall of such information over periods of decades is of questionable accuracy. Although the study-protocol data-analysis plan appropriately addresses exposure-assessment limitations by proposing that exposure be categorized in analysis, the proposed analytic approach calls into question the need for complex water-system modeling. To the extent that simple categories of exposure will be used in the final analysis, the rationale for waiting for complex water modeling to be completed is unclear.

Another major limitation of the study is the inadequate statistical power to detect associations in a plausible range. The selection of specific health end points is the primary reason that power is so limited, so the question arises as to whether they were the most informative outcomes to study. There is some basis for speculating that those outcomes are associated with the solvents of interest largely on the basis of prior epidemiologic studies of water-contamination episodes, but the evidence is not compelling, and there is no reason to believe that these are the "best" choices, given their rarity. The committee's review of the literature on the epidemiology of populations exposed to TCE and PCE (Chapter 5) and the toxicology of the compounds (Chapter 4) did not identify birth defects or childhood cancers as among the outcomes more plausibly related to exposure.

For each of the three outcomes (neural-tube defects, oral clefts, and childhood cancers), there is adequate power only for markedly increased odds ratios (larger than 3). Given current knowledge about the etiologies of these conditions, it is highly unlikely that the exposures that occurred at Camp Lejeune would have increased risk to that degree, regardless of uncertainty about exposure magnitudes. Furthermore, because the investigators also proposed to conduct multivariate analyses to control for the potential impact of other factors on the risk of the conditions, it is important to note that the power of a multivariate analysis will probably be even lower than the estimate for the unadjusted associations.

The data-analysis plan in the protocol is very general and leaves room for the possibility of a proliferation of analyses that will make it more difficult to assess the meaning of any associations that are identified. A detailed written analysis plan specifying primary exposure metrics and key confounders should be prepared in advance of the analysis and should consider alternative approaches to controlling

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confounders. The planned secondary and sensitivity analyses should be discussed more fully in the analysis plan. Because there is interest in multiple exposure periods (for various durations before, during, and after pregnancy), in different approaches to estimating exposure, and in different exposure categories, it is necessary to distinguish the primary exposure metric (such as peak exposure) from those to be evaluated in secondary and sensitivity analyses.

FUTURE STUDIES

An expert panel convened by ATSDR in 2005 judged that additional studies of the Camp Lejeune population would be challenging, perhaps requiring medical evaluation of hundreds of people from widely scattered locations. However, the panel concluded that it might be feasible to conduct a study of mortality outcomes and a study of cancer incidence. Before performing such studies, it recommended that their feasibility be assessed (ATSDR 2005b).

ATSDR has prepared a report on the feasibility of conducting epidemiologic studies to address exposures that occurred at Camp Lejeune (Bove and Ruckart 2008). The report proposed a study of all-cause mortality and a study of cancer incidence by using Department of Defense (DOD) personnel databases to identify a cohort of active-duty marines and Navy personnel who were assigned to Camp Lejeune at any time from June 1975 through December 1985 and a cohort of civilians who worked at the base at any time from June 1974 through December 1985. The agency also proposed to include as a comparison population a sample of active-duty marines and civilians stationed at Camp Pendleton at any time during 1975-1985 who started duty on or after June 1975 and were never stationed at Camp Lejeune during the period of drinking-water contamination. The three cohorts would be considered for inclusion in an all-cause mortality study and a cancer-incidence study, and the Camp Pendleton cohort would serve as an external comparison group for the analysis of civilian and military personnel at Camp Lejeune.

ATSDR proposed to link study participants' residence history on the base with housing records (family housing unit or barracks) to identify participants' drinking-water supply-system history. That would allow inclusion of monthly estimates of water contamination from the water-distribution system in individual-level exposure assessment. For civilian workers, the occupation code and information on the location of each occupation obtained from base staff (such as base industrial hygienists) would be used to link the workplace with the appropriate drinking-water system. Information on length of service on the base obtained from computerized personnel data would be used to estimate the duration of exposure. Marines and civilians assigned to Camp Pendleton would be considered unexposed.

ATSDR's feasibility assessment included a literature review of the health effects of VOCs, particularly TCE and PCE. The review concluded that previous studies supported evaluation of a variety of health effects, predominantly cancers, in future studies at Camp Lejeune. ATSDR's review relied on previous reports by the National Toxicology Program and the National Research Council, occupational studies, and community drinking-water exposure studies. The review identified more health outcomes than described in Chapter 7 of this report, and this suggested a lower threshold for inclusion than applied by the present committee. Both reviews identified kidney cancer, lung cancer, breast cancer, scleroderma, hepatic disease, renal disease, and spontaneous abortion as being of interest. The ATSDR review also suggested that the following outcomes may be important: liver cancer, leukemias, cervical cancer, bladder cancer, esophageal cancer, soft-tissue sarcoma, skin disorders, aplastic anemia, non-Hodgkin lymphoma, multiple myeloma, Hodgkin disease, pancreatic cancer, brain cancer, Parkinson disease, and lupus. The present committee and ATSDR took different approaches to assessing the epidemiologic literature. ATSDR focused on previous reviews and studies that yielded positive results, especially community studies of drinking-water contamination. The committee used an approach developed by the Institute of Medicine (IOM 2003) for reviewing the epidemiologic literature, including consideration of individual study characteristics and biases, synthesis of the available studies, and consideration of evidence from the toxicology literature. Only outcomes that were corroborated and single, very strong studies were flagged as deserving of consideration.

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Health Survey

In January 2008, Congress mandated a Navy-Marine Corps health survey to be conducted in 2009. The survey will be mailed to the active-duty and civilian cohorts at Camp Lejeune, the Camp Pendleton sample, the 12,598 respondents in the 1999-2002 ATSDR survey, and anyone who has registered with the Marine Corps or provided contact information to ATSDR. Items on the survey will include information about any cancer diagnoses (such as type of cancer, date of diagnosis, and state and hospital of diagnosis), residential history, residences on the base, occupational history, and several risk factors (such as socioeconomic status, demographics, smoking, and alcohol consumption). Permission to gain access to medical records will be requested from those reporting cancer diagnoses.

The health survey has the potential to improve future studies of Camp Lejeune residents. For example, the survey would enhance the collection of relevant covariates and expand the potential scope of nonfatal disease and disability beyond what can be addressed in a typical mortality study or in a cancer registry. The health survey would also demonstrate that the health concerns of Camp Lejeune residents are being investigated to the extent feasible. Nevertheless, the committee has several concerns about the health survey as a source of scientifically useful information for assessing the impact of water-supply contamination at Camp Lejeune. First, the statistical power for evaluating relevant outcomes appears to be low and incompletely addressed in the feasibility study. Second, there may be a bias in disease reporting and participation; a person who has a disease or disability may be more likely to participate. ATSDR has determined that for the health survey to be successful, and therefore useful for the proposed studies described below, a participation rate of at least 65% would be necessary. Even with that level of response, there is much potential for participation to be influenced by exposure or disease history. Third, the health survey would include only active-duty personnel and civilians who lived on the base after 1975, not those who were present and exposed before then. Fourth, as previously noted, the quality of exposure data would remain uncertain for the same reasons noted above in connection with the completed and current studies.

All-Cause Mortality Study

The purpose of the mortality study is to evaluate all causes of death in the three cohorts—Camp Lejeune military, Camp Lejeune civilian, and Camp Pendleton military. Followup would begin at the start of known assignment at Camp Lejeune or at the start of active duty for the Camp Pendleton cohort and continue to the end of the study period (December 31, 2007) or death.

Cause-specific mortality in the cohorts would be compared with national rates by using standardized mortality ratios and standardized mortality ORs. ATSDR also proposes to compare those exposed to contaminated drinking water at Camp Lejeune with those unexposed at Camp Pendleton to minimize bias due to the healthy-veteran effect caused by differences in underlying mortality between veterans and the general public (Bove and Ruckart 2008). ATSDR considered conducting internal comparisons between exposed and unexposed groups at Camp Lejeune but rejected such analysis because of the small number of subjects at Camp Lejeune who were free of exposure. Finally, the agency proposed to consider lagging exposures in the analyses to account for a latent period.

Because individual-level information on potential confounders is not available in the computerized databases used to identify study subjects, ATSDR proposes two approaches to consider potential confounders. If the Navy-Marine Corps health survey is deemed successful, it will use information from the survey participants to adjust for confounding in a two-stage approach, extrapolating the information from the health survey for application to the mortality study. If the survey does not generate an adequate response, consideration will be given to nested case-control sampling with interviews of decedents' next of kin to determine information on risk factors. Those are reasonable strategies but are of unknown feasibility.

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Cancer-Incidence Study

The cancer-incidence study would evaluate all confirmed cancers diagnosed in the active-duty and civilian worker cohorts at Camp Lejeune and Camp Pendleton and the cohort of survey participants. Because the number of women in the active-duty cohort is small, an additional 2,900 women who lived on the base and were identified through their participation in the birth-defects and childhood-leukemia study would be added to the Camp Lejeune active-duty cohort. To identify cancer cases, ATSDR proposed to match each cohort member's personal identification information to the available data on cancers in all 50 state cancer registries (or at least the cancer registries from the 25-30 states with the highest percentages of known retirees), the DOD, and Department of Veterans Affairs (VA) cancer registries, the Naval Health Research Center's Career History Archival Medical and Personnel System (CHAMPS), death certificates, and the National Death Index. Followup would begin with the start of each registry's operation or 1975, whichever is later, and continue until December 31, 2007. If the Navy-Marine Corps health survey is successful, the cancer-incidence study would also include participants in the survey. Personal identification information on the survey participants will be matched to available data on cancer in the state, DOD, and VA cancer registries. Therefore, like the mortality study, the incidence study will use a two-stage approach in which information on exposure and cancer would be available on everyone in the study who is not lost to followup, but information on individual-level potential confounders will be available only on those who complete the health survey. That information will be used to adjust for confounding in the analyses of the entire study population.

Because all state cancer registries have data available from 1997 on, cancer incidences in the Camp Lejeune and Camp Pendleton cohorts will be compared with national incidences for the period 1997-2007. Comparisons between the exposed and unexposed participants stationed at Camp Lejeune and comparisons between Camp Lejeune and Camp Pendleton would use all cancers identified from 1975 to 2007—the entire study period.

Other Future Studies

ATSDR will also consider studying nonfatal, noncancer diseases. The Navy-Marine Corps health survey would include questions on nonfatal diseases and symptoms that are known to be or suspected of being associated with solvent exposure. Such diseases as Parkinson disease, renal failure and other severe renal diseases, severe hepatic diseases, lupus, and scleroderma will be asked about directly, and space will be provided so that respondents can report other disease conditions. Symptom ascertainment may include questions on skin disorders and neurologic disorders. All those diseases and conditions can be confirmed by using medical records. The CHAMPS database can also be used to identify and confirm diseases occurring in marines on active duty from 1980 on. However, ATSDR states that a study using that database would probably have insufficient statistical power and therefore the study is of very low priority.

Review and Evaluation

ATSDR proposed to conduct morbidity and mortality studies that would address some of but not all the questions that have been raised by the affected community. The health end points to be considered would include fatal conditions that are sufficiently common for analysis (depending on the success of the mortality study), incident cancers (depending on the success of the cancer-incidence study), and nonfatal diseases of interest other than cancer, such as scleroderma and neurologic deficits (depending on the success of the health survey). The mortality study is very likely to be feasible, given the documentation of data sources in the ATSDR feasibility assessment, whereas it is not clear that the cancer-incidence study would be successful in engaging and linking with all 50 state registries. The health survey is subject to uncertain response, as noted by ATSDR, which may limit its value.

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ATSDR recognized that it is necessary to focus on health conditions that are sufficiently common to allow useful epidemiologic evaluation. It conducted a series of sample-size calculations to ensure that there would be sufficient statistical power to evaluate associations of exposure with prevalent cancers and all-cause mortality with a 10-year lag in exposure (Bove and Ruckart 2008). It is not clear whether there is sufficient power for comparisons of the Camp Lejeune and the Camp Pendleton cohorts, nor is it clear whether outcomes of particular interest to ATSDR and to the committee (such as kidney cancer) can be evaluated with adequate power. ATSDR has begun to consider the adequacy of statistical power, but the information and interpretation fall short of making a clear case that the study methods, even if successful, would generate adequate power for the comparisons of interest.

ATSDR recognized the potential for confounding due to unmeasured risk factors in both the mortality and cancer-incidence studies. With the exception of age, sex, and race, individual-level factors in the populations of Camp Lejeune and Camp Pendleton are not available. However, some information on the population that completes the health survey would be available. ATSDR proposes a two-stage approach, using the survey data to estimate the effects of confounding with reference to the cohort as a whole. How that would be performed is not described in detail (that is, on an individual basis or by applying patterns of confounding from the health survey to the mortality and cancer-incidence studies). It also is not clear whether the survey will be adequately designed to provide information on the Camp Pendleton cohort that is comparable with that on the Camp Lejeune residents. As ATSDR notes, the value of those data is contingent on generating an adequate response. The use of nested case-control studies of deaths from causes of interest with interviews of next of kin to assess confounding is an alternative approach that is feasible but quite demanding in that it will be necessary to locate, recruit, and interview the next of kin after identification of deaths or incident cancers.

ATSDR recognized the potential for bias in the assessment of exposures because of uncertainties in identifying locations on the base where cohort members were stationed and because of possible exposure to drinking-water contaminants at other than primary residences or work locations. The agency suggested that such bias would tend to underestimate the disease risk associated with exposure if exposure actually causes the disease. ATSDR was confident that the extensive water modeling that is being done at the base would reduce the effect of exposure-misclassification bias that might occur. The committee has less confidence in the certainty of the modeling efforts, given the small number of water-supply measurements available for validating the models (see Chapter 2). ATSDR has discussed basing the exposure assessment on the monthly concentrations of contaminants in the drinking water at either the residences or the workplace locations, as appropriate. However, there has been no discussion of the exposure metric that would be calculated and linked with outcomes. For example, it was unclear whether ATSDR would assess the effect of cumulative exposure or of peak exposure.

Advantages of the cancer-incidence study over the mortality study, as described by ATSDR, are the higher number of cancer cases and the ability to assess etiology independently of survival. Several female cancers (breast, ovarian, cervical, and uterine) could be evaluated with adequate statistical power (Bove and Ruckart 2008). However, there are concerns about the comparability of the women at Camp Lejeune, who include spouses of workers and women identified because of having given birth, compared with those identified at Camp Pendleton. The cancer-incidence study would also have greater power to detect associations with a broader array of cancers of interest (such as kidney, non-Hodgkin lymphoma, and leukemia) and would eliminate potential effects of differential survival. ATSDR discussed the possibility of missed cancers in the incidence study due to incomplete coverage of the study period by the individual state cancer registries. As it noted, there should be no bias in the internal comparisons, because missing cases are unlikely to be associated with exposure status. However, the comparison between Camp Lejeune and Camp Pendleton could be affected if there are differences between the bases in the percentage of retired marines migrating to states whose cancer registries are older, and there are broader concerns about the constitution of the study populations and the multiple ways in which the Camp Lejeune cohort would be assembled.

In summary, although the major issues bearing on the feasibility of the proposed studies have been considered by ATSDR and the approach has some strengths, notably inclusion of a comparable ma-

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rine base, there are serious unresolved questions about the feasibility and ultimate value of the studies. It is not clear that the cancer-incidence study or the health survey would be successful; success in the former would be contingent on the cooperation of many cancer registries, and success of the latter on generating an adequate response. The statistical power to compare groups of interest across the array of outcomes of interest was not provided. The ultimate ability to measure and adjust for potential confounding factors is not certain, nor is it clear how the information from the health survey would be applied to the study cohorts. With those concerns layered on the previously noted problems regarding the accuracy of exposure assessment, it is not clear what the scientific value of additional studies would be.

FINDINGS OF COMPLETED, CURRENT, AND FUTURE STUDIES

The committee considered the value of completed, current, and planned studies of the Camp Lejeune population in light of the information available on assessing exposure, health end points of primary concern, and what is known about the potentially affected population from previous studies and work in progress. Review of data and modeling efforts pertaining to exposure provided clear documentation that contaminants were present but provided little basis for suggesting that exposures of the population can be reconstructed with much precision. The literature on potential health effects of the agents of primary concern, TCE and PCE (see Chapters 4 and 5), indicates an array of possible health effects, including cancers, reproductive effects, neurobehavioral effects, immunologic effects, and renal and hepatic toxicity, possibly affecting both children and adults.

Completed and current research at Camp Lejeune has been limited to particular end points and focused on pregnancy outcomes—including fetal growth, preterm birth, and birth defects—and childhood cancers. Those studies have not distinguished and are unlikely to be able to distinguish between an absence of adverse effects and the presence of modest effects that fall below the limits of what can be identified in light of exposure misclassification and low statistical power. A broader consideration of health effects would be needed to provide scientific evidence to answer questions regarding the possible effects of water-supply contamination. For new studies to make a substantial contribution to evaluating whether exposure to contaminated water resulted in adverse health effects, an array of feasibility considerations needs to be addressed and resolved favorably. ATSDR has made a reasonable effort to evaluate those issues in the study of the feasibility of future work, but structural problems make it difficult to show that such research will be of high scientific merit. Key feasibility considerations that apply to all environmental epidemiology studies, including the evaluation of water contaminants and health at Camp Lejeune, are listed below.

- *Study population*. The residents of Camp Lejeune potentially exposed to the contaminated water supplies of concern need to be enumerated for study, with inclusion of exposed people and comparable unexposed people identified from elsewhere on the base, from periods beyond the years of contamination, or from other military bases.
- *Exposure*. The water serving the homes of the individual residents at specific times would need to be identified to assess potential exposure to specific toxicants. There would need to be an independent process of exposure assessment that allows estimation of concentrations of specific pollutants going from the source to the tap and related to specific time and places. It would then be necessary to reconstruct residential histories in Camp Lejeune to link people to estimated water concentrations of pollutants in their homes. Ideally, studies would consider water sources at the locations of work, day care, and schools and consider individual behavior, including water consumption and bathing.
- *Statistical power*. The health outcomes of interest vary greatly in frequency of occurrence. For research results to be informative, sufficient numbers of exposed and unexposed people are needed to generate stable estimates of rates of diseases and to make comparisons. Disease latency—the time between exposure and development and manifestation of disease—is important. The Camp Lejeune population was generally young, so even with the passage of 20 or more years since exposure onset, they are still not

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at the ages at which some of the specific diseases of concern are commonly observed. Given the size and age distribution of the population, it may be infeasible to focus on such end points as kidney cancer, although it is justified on the basis of independent research as reflected in the toxicology and epidemiology literature. Furthermore, given the brevity of many people's residence on the base, realistic effect sizes would need to be considered in assessing adequacy of statistical power.

- *Potential confounders*. The potential for confounding of the observed effects of water exposure by other factors that affect disease incidence would need to be addressed. Because residence or workplace on the base is a primary determinant of exposure and may be related to rank, seniority, or job duty, which themselves may be markers of disease risk, they would need to be measured and adjusted for in the analysis. More direct markers of disease risk—such as tobacco and alcohol use history, body-mass index, and diet—would also need to be addressed for selected health end points, including those of primary concern (such as renal disease).
- *Time and cost*. Realistic estimates of the time required to conduct the study are needed, particularly in light of the long history of concerns regarding contaminated water and health at Camp Lejeune. The financial cost is also a key consideration in that studies that require generating large volumes of new data through individual contact and advanced water modeling are expensive and time-consuming.
- *Credibility of findings*. It is important not only that the research be scientifically rigorous but that the results be fully and widely accepted. That issue would need to be addressed from the outset in framing the question, the mechanism of funding, the selection of the researchers, the conduct of the study, and the interpretation, evaluation, and dissemination of results.

For structural reasons, meeting the criteria above is problematic. One major problem is that the number of people available for the study may be too small to generate statistically meaningful results related to rare outcomes of greatest interest (such as kidney cancer). Historical contaminant-exposure estimates are difficult to construct and might be impossible to quantify with any confidence in the absence of contaminant measurements taken during the period of concern, no matter how elaborate the water models are. Many residents were exposed for relatively short periods; most lived in the affected areas for only a few years (2-3 years was typical for marines stationed at the base), and it is difficult to know what types of exposures they had before or after they lived at Camp Lejeune. We know that there were some highly contaminated wells for some periods, but their operations were cycled with those of uncontaminated wells, so exposure to water contaminants was intermittent and cannot be determined on an individual basis or for time frames of weeks as required to assess the occurrence of reproductive health end points. Even if all the information on the population, exposure, and health outcomes could be obtained, consideration should be given to whether the cost and time required to conduct more definitive studies justify the likely delay in or distraction from resolving the public-health concerns and the controversy that has developed around the issue. The costs and benefits of such efforts need to be reconciled. Finally, the long-standing controversy over this episode is apparent, and some question the objectivity of the Marine Corps in generating valid, objectively interpreted scientific data on the topic. Future research needs to be both scientifically informative and credible to the multiple target audiences.

CONCLUSIONS AND RECOMMENDATIONS

The scope of health outcomes addressed in completed and current studies of the Camp Lejeune population is limited and driven, to a large extent, by the types of diseases that are feasible to measure with available surveillance data and a health survey. They are not necessarily the conditions or diseases that would be considered of highest priority on the basis of the committee's review of the literature of epidemiology and toxicology. There are serious limitations in the quality of existing studies of the Camp Lejeune population. Consequently, those studies provide little information to assess directly whether the population exposed to water contaminants has suffered adverse health effects of them. Completion of the studies in progress will provide only a marginal improvement in understanding.

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Recommendations:

- The planned reanalyses of the preterm-birth and fetal-growth study should be completed as soon as possible, taking advantage of the corrected exposure information that is available but not awaiting more extensive water modeling. Reanalyses should include development of a detailed written analysis plan (for example, Sheppard 2008). Careful attention should be paid to confounding, given the associations between residence and indicators of risk. Given the inherent limitations of birth-certificate data, sensitivity analyses to address gestational-age misclassification, subgroup analyses, and confounding should be incorporated. Finally, future reports should provide full details of the approach, results, and sensitivity analyses; the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines (Vandenbroucke et al. 2007) would be suitable for such documentation. Despite the limited scientific benefit of this effort, the modest cost justifies its prompt completion.
- The current case-control study of birth defects and childhood cancer should be completed, given the effort already invested, despite severely limited statistical power. The same recommendations noted for the study of preterm birth and fetal growth apply here as well, including careful planning of analytic methods and full documentation. Relative to the overall effort expended thus far, the committee recognizes the need for completion of this study.

It could be argued that additional studies of the potential health effects from the historical contamination of drinking water at Camp Lejeune could help guide decisions on how to resolve the claims of former residents. Beyond its scientific merit, a more thorough evaluation of health patterns of former Camp Lejeune residents could be seen as providing a valuable public-health service in providing documentation of the experience of former residents and perhaps characterizing the population better. However, on the basis of what is known about the contamination of water supplies at Camp Lejeune; the size, age, and residential mobility of the residents; and the availability of records, the committee concludes that it would be extremely difficult to conduct direct epidemiologic studies of sufficient quality and scope to make a substantial contribution to resolving the health concerns of former Camp Lejeune residents. Conduct of research that is deficient in those respects not only would waste resources but has the potential to do harm by generating misleading results that erroneously implicate or exonerate the exposures of concern.

Recommendations:

- New studies should be undertaken only if their feasibility and promise of providing substantially improved knowledge on whether health effects have resulted from water exposure at Camp Lejeune are established in advance.
- Decisions regarding the appropriate policy response to health concerns about exposure to contaminated water at Camp Lejeune should not be delayed or await the results of epidemiologic studies that are in progress or planned inasmuch as those studies are unlikely to provide definitive information on potential health effects.

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Appendix A

Biographic Information on the Committee on Contaminated Drinking Water at Camp Lejeune

David A. Savitz *(Chair)* is the Charles W. Bluhdorn Professor in the Department of Community and Preventive Medicine at the Mount Sinai School of Medicine. He also serves as director of the Disease Prevention and Public Health Institute. His research interests are in reproductive, environmental, and cancer epidemiology. Dr. Savitz was president of the Society for Epidemiologic Research and the Society for Pediatric and Perinatal Epidemiologic Research and was the North American regional councilor for the International Epidemiological Association. He has served on several Institute of Medicine (IOM) and National Research Council committees, including being chair of the Committee on Making Best Use of the Agent Orange Exposure Reconstruction Model. Past service includes the Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds and the Committee on Understanding Premature Birth and Assuring Health Outcomes. He serves on the Committee to Reexamine IOM Pregnancy Weight Guidelines. Dr. Savitz received his MS in preventive medicine from Ohio State University and his PhD in epidemiology from the University of Pittsburgh. He was elected to membership in IOM in 2007.

Caroline L. Baier-Anderson is a health scientist with the Environmental Defense Fund and an assistant professor in the Department of Epidemiology and Preventive Medicine of the University of Maryland, Baltimore (UMB). Her research interests are in the use of science in risk assessment and environmental decision-making, exposure assessment, multistakeholder problem-solving for complex environmental issues, and risk communication. Past work has included providing technical outreach assistance to communities adjacent to hazardous-waste sites and working with the U.S. Environmental Protection Agency (EPA) and the U.S. Army on the cleanup of Superfund sites at Aberdeen Proving Ground. She has consulted on risk assessments of solvent-contaminated groundwater. Dr. Baier-Anderson received her PhD in toxicology from UMB.

James V. Bruckner is a professor in the Department of Pharmaceutical and Biomedical Sciences of the University of Georgia College of Pharmacy. His research interests are in the pharmacokinetics and toxicologic and carcinogenic potential of volatile organic compounds, including trichloroethylene (TCE) and tetrachloroethylene. His current efforts are directed toward developing physiologically based pharmacokinetic models of TCE and its interactions with alcohol. Dr. Bruckner has served on several National Research Council committees, including the Committee on Acute Exposure Guideline Levels and the Committee on Use of Third Party Toxicity Research with Human Test Subjects. He received his MS from the University of Texas at Austin and his PhD in toxicology from the University of Michigan.

Prabhakar Clement is a professor of environmental engineering and Arthur H. Feagin Chair of Civil Engineering at Auburn University. Before joining the university, he worked as a senior research engineer

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at the Pacific Northwest National Laboratory for 6 years and then as a senior lecturer in the Department of Environmental Engineering at the University of Western Australia for 3 years. His research interests are in modeling of water flow and reactive-contaminant transport in groundwater systems, bioremediation of contaminated aquifers, numerical modeling of environmental processes, water-quality modeling, and optimal design of treatment systems. He is a member of the Groundwater Quality Committee of the American Society of Civil Engineers (ASCE) and served as the associate editor of ASCE's *Journal of Hydrologic Engineering* and the *Journal of Contaminant Hydrology*. Dr. Clement received his MSc in physics from Madurai University, his MTech in environmental sciences and engineering from the Indian Institute of Technology, Bombay, and his PhD in civil engineering from Auburn University. He is a registered professional civil engineer.

Carole A. Kimmel is a consultant in toxicology and risk assessment, particularly in reproductive and developmental effects. She was a senior scientist for 20 years with the National Center for Environmental Assessment at the U.S, Environmental Protection Agency (EPA). She spent her career at EPA working on advances in risk assessment for noncancer health effects, including reproductive and developmental toxicity and neurotoxicity. Dr. Kimmel cochaired the Developmental Disorders Working Group of the President's Task Force on Environmental Health Risks and Safety Risks to Children and was a leader in an interagency effort to plan and implement the National Children's Study. She is a former president of the Teratology Society and of the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology. Her current consulting work includes a part-time position with Exponent as a senior managing scientist and continued involvement in the National Children's Study. Dr. Kimmel received her PhD in anatomy and teratology from the University of Cincinnati.

Francine Laden is an assistant professor of environmental epidemiology at the Harvard School of Public Health and assistant professor of medicine at the Channing Laboratory of Brigham and Women's Hospital and Harvard Medical School. Her research interests are in the environmental epidemiology of cancer and respiratory disease. Her current research is focused on analyses of the relationship between organochlorines and non-Hodgkin lymphoma and Parkinson disease; lung cancer and cardiovascular mortality and diesel exhaust in the Trucking Industry Particle Study; ambient air pollution and cardiopulmonary disease in the Nurses' Health Study; and mortality followup in the Harvard Six Cities Study. Dr. Laden was a member of the Institute of Medicine Committee on Gulf War and Health: Review of the Medical Literature Relative to Gulf War Veterans' Health. She received her MS in environmental health management and her ScD in epidemiology from the Harvard School of Public Health.

Bruce P. Lanphear is a senior scientist at the Child & Family Research Institute and professor of Children's Environmental Health at Simon Fraser University, both in British Columbia, Canada. He is the principal investigator for a study of fetal and early-childhood exposure to prevalent environmental neurotoxins—including lead, alcohol, pesticides, mercury, polychlorinated biphenyls, and environmental tobacco smoke—funded by the National Institute of Environmental Health Sciences and the Environmental Protection Agency (EPA). Dr. Lanphear has conducted numerous epidemiologic studies and randomized controlled trials of environmental hazards, including the use of high-efficiency particulate air cleaners to reduce asthma symptoms and lead-hazard controls to prevent childhood lead exposure. His research also explores gene-environment interactions to enhance understanding of susceptibility to environmental pollutants. He recently served on EPA's Clean Air Scientific Advisory Committee for the national ambient air quality lead standard. He received his MD from the University of Missouri-Kansas City, and his MPH from the Tulane University School of Public Health and Tropical Medicine.

Xiaomei Ma is an assistant professor in the Department of Epidemiology of the Yale School of Public Health. Her research interests are in the epidemiology of malignancies of the human hematopoietic system. Specifically, she is interested in environmental and genetic factors in the etiology of childhood leukemia, the epidemiology of myeloproliferative disorders, and methodologic issues in the design of epi-

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demiologic studies. Dr. Ma received her MS from Shanghai Medical University and her PhD in epidemiology from the University of California, Berkeley.

John R. Nuckols is a professor in the Department of Environmental and Radiological Health Sciences of Colorado State University. He is also director of the Environmental Health Advanced Systems Laboratory. His research interests are in exposure assessment in population-based environmental health studies using computer simulation modeling and spatial information systems. Dr. Nuckols received his MS in civil engineering from Northwestern University and his PhD in engineering from the University of Kentucky.

Andrew F. Olshan is a professor in and chair of the Department of Epidemiology of the University of North Carolina School of Public Health. His research interests are in the etiology of birth defects and cancer in children. His recent work has focused on the role of paternal exposure and adverse health effects in children, risk factors for birth defects and Wilms tumor in children, and the effects of drinking-water disinfection byproducts on male reproductive health. He has served on several Institute of Medicine committees, most recently the Committee for Review of Evidence Regarding Link between Exposure to Agent Orange and Diabetes. Dr. Olshan received his MS and PhD in epidemiology from the University of Washington.

Lianne Sheppard is a professor in the Department of Biostatistics and the Department of Occupational and Environmental Health Sciences at the University of Washington School of Public Health. She is also an affiliate member of the Fred Hutchinson Cancer Research Center. She is an elected fellow of the American Statistical Association and serves as an expert panelist on the ozone, NO_x, and SO_x review panels the U.S. Environmental Protection Agency Clean Air Scientific Advisory Committee. Her scientific interests include estimating the health effects of occupational and environmental exposures, air-pollution health effects, observational-study design, and group information in observational studies. She is an active co-investigator in several occupational-health and environmental-health studies, particularly in air pollution and occupational noise exposure. Her statistical-methods research addresses the role of exposure and study design in estimating health effects in observational studies. Dr. Sheppard received her ScM in biostatistics from Johns Hopkins University and her PhD from the University of Washington.

Elaine Symanski is an associate professor in the Division of Epidemiology and Disease Control of the University of Texas School of Public Health. Her research interests are in the development and application of quantitatively based approaches for evaluating occupational and environmental exposure, retrospective exposure assessment, and investigation of health effects associated with exposure in workplace and community settings. Dr. Symanski received her MSPH and PhD in environmental sciences and engineering from the University of North Carolina at Chapel Hill.

Janice W. Yager is an adjunct professor in the Department of Internal Medicine, Division of Epidemiology and Statistics, of the University of New Mexico School of Medicine. Her current research interests are in application of biomarkers in epidemiology and the development and impact of increased knowledge in toxic modes of action on reducing uncertainties in risk assessment with specific interest in solvents and metals. Before joining the university, she initiated, managed, and provided scientific contributions to research programs and projects in environmental and occupational health sciences at the Electric Power Research Institute (EPRI). Before joining EPRI, Dr. Yager was associate research toxicologist and lecturer in the Department of Environmental Health Sciences of the School of Public Health of the University of California, Berkeley and was a National Institutes of Health visiting scientist to the Academy of Finland. She has served as president and member of the Executive Committee of the Genetic and Environmental Toxicology Association, on the Board of Councilors of the Environmental Mutagen Society, and on a number of scientific advisory committees, including the American Conference of Governmental Industrial Hygienists Biological Exposure Indices Committee and the U.S. Environmental Protection

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Agency (EPA) External Program Peer Review Committee Carcinogenesis Section. Dr. Yager was a member of the National Research Council Committee on Human Health Risks of Trichloroethylene and EPA's Scientific Advisory Board Arsenic Review Panel. She received her MPH and PhD in environmental health sciences from the University of California, Berkeley.

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Appendix B

Participants at Public Sessions

September 24, 2007, Washington, DC

Persons who made formal presentations

Major General (Select) Eugene G. Payne, Jr., Assistant Deputy Commandant Installations and Logistics (Facilities), Headquarters Marine Corps
Kelly Dreyer, Headquarters Marine Corps
Marcia Crosse, U.S. Government Accountability Office
Frank Bove, Agency for Toxic Substances and Disease Registry
Morris Maslia, Agency for Toxic Substances and Disease Registry
Jerry Ensminger

Persons who made comments at open-microphone session

Jeff Byron, The Few, the Proud, the Forgotten

Attendees

Brynn Ashton, U.S. Marine Corps
Cheryl Siegel Scott, U.S. Environmental Protection Agency
Chris Rennix, Navy Environmental Health Center
John Sludden
Ken Stier
Lita Hyland
Marie Roda, Roda Creative
Mary A Simmons, Navy Environmental Health Center
Paul Dugard, HSIA
Shannon Ensminger, Roda Creative
Steve Risotto, HSIA
Yvonne Walker, Navy Environmental Health Center

November 15, 2007, Camp Lejeune, NC

Persons who made formal presentations

Mary Hill, U.S. Geological Survey
Richard Clapp (via conference call)

Persons who made comments at open-microphone session

Cindy Cribb, Private citizen
Col. Michael E. Williams, USCG Training Center

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Curtisteen Hill, Private citizen
Eli Sharpless
Jeff Byron, The few, the proud, the forgotten (website coordinator)
Jerry W. Townsend, retired
Kris L. Thomas, Private citizen
Marilyn Wallace, retired civilian
Mary Walton Freshwater, USMC
Nellie Bell, retired civilian
Paula Lawrence, Dep
Terry Dyer, the Stand

Attendees

Angelo Inglisa
Ann G. Turner
Betty Reed
Brad I. Walker, Lighthouse Films
Catherine Maria Keener, WHQR Public Radio
Chelsea Donovan, WITN
Clifton Jones, Jr.,
David Steinberger, CBS news
Erika Maureen DuChien
Eugene Shelton, WCTI-TV
Frances Midgett Hollowell
Gareth J. McGrath, Wilmington Star-News
James H. Middleton
James Highsmith
Jennifer Elise Hlad, Jacksonville Daily News
Joy Barker
Louise Jigettes
Marilyn Mejarado
Michael Sean Partain
Mike Spencer, Wilmington Star-News
Morris Levi Maslia, Agency for Toxic Substances and Disease Registry
Rachel E Libert, Tied to the Tracks Films, Inc
Reginald Huff, CBS news cameraman
Robert Keven Thomas
Sandra H. Bridges, CAP member for ASTSDR
Steve Goyas
Vianna Witcher

September 12, 2008, Washington, DC

Persons who made formal presentations

Frank Bove, Agency for Toxic Substances and Disease Registry
Persons who made comments at open-microphone session

Jeff Byron, The Few, the Proud, the Forgotten (website coordinator)

Attendees

Harold Graef, U.S. Marine Corps
Mary Byron
Mike Tencate, U.S. Marine Corps
Scott Williams, U.S. Marine Corps

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Appendix C

Supplemental and Supporting Data for Chapter 2

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TABLE C-1 Characteristics of Remedial Investigation Sites Outside Tarawa Terrace and Hadnot Point Water-Supply Areas[a]

Water-Supply Area	Operable Unit, RI Site	Site Description	Nature of Waste or Contamination	Groundwater Contaminants Identified
Stone Bay Rifle Range	OU 14, site 69	Rifle range, chemical dump	Disposal of chemical wastes: PCBs, solvents, pesticides, tear gas or other training agents	VOCs in groundwater
Stone Bay Rifle Range	Pre-RI site 68	Rifle range, dump	Disposal of mixed wastes: garbage, building debris, waste treatment sludge, solvents	Low concentrations of organics in groundwater
Camp Geiger/MCAS	OU 3, site 48	MCAS mercury dump	No contaminants identified	No groundwater contamination
Camp Geiger/MCAS	OU 4, site 41	Camp Geiger dump near former trailer park	Mixed-waste dump containing solvents, batteries, ordnance and chemical training materials, construction waste, petroleum waste, pesticides	Metals (chromium, iron, lead, manganese) in groundwater
Camp Geiger/MCAS	OU 6, site 36	Camp Geiger dump area	Mixed industrial waste	VOCs in groundwater
Camp Geiger/MCAS	OU 6, site 43	Agan Street dump	Construction debris, sewage sludge, semivolatiles, pesticides	No significant groundwater contamination
Camp Geiger/MCAS	OU 6, site 44	Jones Street dump	Construction debris, paint, pesticides	Contaminated groundwater (VOCs) traced to other sites (OU 16)
Camp Geiger/MCAS	OU 6, site 54	Fire training-burn pit for airport	Unlined pit used until 1975 for burning VOCs	VOCs, SVOCs
Camp Geiger/MCAS	OU 10, site 35	Camp Geiger fuel farm	Fuel storage-tank releases	Multiple fuel, solvent plumes
Camp Geiger/MCAS	OU 16, 89	Camp Geiger area UST	Fuel storage-tank releases	Fuel contamination
Camp Geiger/MCAS	OU 16, 93	Camp Geiger area UST	Fuel storage-tank releases	Fuel contamination
Camp Geiger/MCAS	OU 20, site 86	Tank area, storage for petroleum products	Fuel storage-tank releases	VOC, SVOC contamination
Camp Geiger/MCAS	Pre-RI, site 75	MCAS basketball-court site	Reported drum burial—never found	No contamination
Camp Geiger/MCAS	Pre-RI, site 76	MCAS Curtis Road site	Reported drum burial—never found	No contamination
Camp Geiger/MCAS	Pre-RI, site 87	MCAS officer housing area dump	Hospital wastes eroding from bank	No groundwater contamination
Camp Johnson	OU 8, site 16	Monford Point burn dump	Housing trash, vehicle staging area	No significant groundwater contamination
Camp Johnson	Pre-RI, site 85	Camp Johnson battery dump	Battery disposal, metals in soils	No significant groundwater contamination
Holcomb Blvd.	OU 4, site 74	Mess hall grease-disposal area	Disposal area for pesticides, chemical-warfare materiel	Low concentrations of pesticides in one monitoring well

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Holcomb Blvd.	OU 5, site 2	Former nursery, day-care center	Former pesticide storage area with soil contamination	Low concentrations of toluene, ethylbenzene
Holcomb Blvd.	OU 11, site 80	Paradise Point golf maintenance area	Pesticides in soil	No significant groundwater contamination
Holcomb Blvd.	OU 12, site 3	Old creosote plant	Residual creosote contamination	VOCs, PAHs in groundwater
Holcomb Blvd.	OU 19, site 84	Building with PCBs, petroleum wastes	Building, soil contamination	No significant groundwater contamination
Courthouse Bay	OU 9, site 65	Engineer dump	Battery-acid, petroleum-product disposal	No significant groundwater contamination
Courthouse Bay	OU 17, sites 90, 91, 92	Courthouse Bay UST storage area	Fuel-storage tank releases	Fuel, solvent contamination from site 90 only
Courthouse Bay	OU 21, site 73	Courthouse Bay liquid-disposal area	Waste-oil , battery-acid disposal	VOCs in groundwater

[a]Data abstracted from Baker Environmental, Inc (1999), CH2M Hill and Baker Environmental, Inc (2005).
Abbreviations: MCAS = Marine Corps Air Station, OU = operable unit, PAH = polycyclic aromatic hydrocarbon, RI = remedial investigation, SVOC = semi-volatile organic compound, UST = underground storage tank, VOC = volatile organic compound.

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TABLE C-2 Documents That Contain Water-Quality Testing Information

CLW Documents				JTC Reports Not in CLW Documents		CMC Panel Summary
ALL	Hadnot Point	Tarawa Terrace	Holcomb Blvd.	Report	JTC Report	Document References
14RDENR300490	CLW0436	14RDENR300490	CLW1054	226	86-072	14 R DENR 300490
21RDENR000992	CLW0438	21RDENR000992	CLW1426	229	86-088	21 R DENR 000992
57MDENR050686	CLW0441	57MDENR050686	CLW1650	231	86-092	57 M DENR 050686
CLW 0430	CLW0443	CLW0592	CLW4512	237	86-094	
CLW 0436	CLW0444	CLW0606	CLW4513	243	86-112	
CLW 0438	CLW0446	CLW0694	CLW4516	251	86-122	
CLW 0441	CLW0543	CLW0952	CLW4533	253	86-140	
CLW 0443	CLW0566	CLW1124	CLW4546	259	86-142	
CLW 0444	CLW0580	CLW1182	CLW4558	261	86-143	
CLW 0446	CLW0592	CLW1183	CLW4708	273	86-211	
CLW 0487	CLW0596	CLW1232	CLW4709	275	86-212	
CLW 0495	CLW0606	CLW1244	CLW4787	275	86-212	
CLW 0498	CLW0694	CLW1283	CLW5369	286	86-265	
CLW 0500	CLW0952	CLW1355	CLW5371	289	86-278	
CLW 0503	CLW1051	CLW1426	CLW5484	298	86-276	
CLW 0508	CLW1054	CLW1475	CLW5509	302	86-323	
CLW 0511	CLW1089	CLW1557	CLW5594	308	86-324	
CLW 0514	CLW1093	CLW2979		316	86-329	
CLW 0543	CLW1283	CLW4513		320	86-347	
CLW 0566	CLW1426	CLW4546		333	86-381	
CLW 0580	CLW1647	CLW4558		341	86-398	
CLW 0592	CLW1650	CLW4707		345	86-410	
CLW 0596	CLW1652	CLW4787		346	86-411	
CLW 0606	CLW1796	CLW4806		353	86-422	
CLW 0694	CLW1917	CLW5082		358	86-453	
CLW 0952	CLW3256	CLW5094		363	86-464	
CLW 1051	CLW4512	CLW5102		493	87-001	
CLW 1054	CLW4513	CLW5131				
CLW 1089	CLW4516	CLW5362				
CLW 1093	CLW4533	CLW5452				
CLW 1124	CLW4546	CLW5478				
CLW 1182	CLW4558	CLW5484				
CLW 1183	CLW4708	CLW5509				
CLW 1232	CLW4709	CLW5529				
CLW 1244	CLW4787	CLW5565				
CLW 1283	CLW4976	CLW5570				
CLW 1355	CLW5102	CLW5839				

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(Continued)

CLW 1426
CLW 1475
CLW 1557
CLW 1647
CLW 1650
CLW 1652
CLW 1796
CLW 1917
CLW 2979
CLW 3256
CLW 3679
CLW 3689
CLW 3736
CLW 3745
CLW 4512
CLW 4513
CLW 4516
CLW 4533
CLW 4546
CLW 4558
CLW 4707
CLW 4708
CLW 4709
CLW 4787
CLW 4806
CLW 4976
CLW 5082
CLW 5094
CLW 5102
CLW 5112
CLW 5123
CLW 5131
CLW 5146
CLW 5156
CLW 5169
CLW 5362
CLW 5369
CLW 5371
CLW 5452

CLW5112
CLW5123
CLW5131
CLW5146
CLW5369
CLW5371
CLW5452
CLW5478
CLW5509
CLW5594
CLW5632
CLW5644
CLW5658
CLW5664
CLW5669
CLW5839
CLW5849
CLW5868
CLW5881
CLW5892
CLW6285
CLW6339

CLW5849
CLW5868
CLW5881
CLW5892
CLW6339

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TABLE C-2 Continued

CLW Documents				JTC Reports Not in CLW Documents		CMC Panel Summary
ALL	Hadnot Point	Tarawa Terrace	Holcomb Blvd.	Report	JTC Report	Document References
CLW 5478						
CLW 5484						
CLW 5509						
CLW 5529						
CLW 5539						
CLW 5565						
CLW 5570						
CLW 5594						
CLW 5632						
CLW 5644						
CLW 5658						
CLW 5664						
CLW 5669						
CLW 5839						
CLW 5845						
CLW 5849						
CLW 5861						
CLW 5868						
CLW 5877						
CLW 5881						
CLW 5888						
CLW 5892						
CLW 6039						
CLW 6075						
CLW 6124						
CLW 6285						
CLW 6339						

Abbreviation: CLW = Camp Lejeune water.
Source: U.S. Marine Corps, personal commun., September 15, 2008.

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WATER-SAMPLING DATA IN TABLES C-3 AND C4

The committee reviewed Camp Lejeune water (CLW) documents for water-quality sample information relevant to Hadnot Point. The Marine Corps provided guidance on which CLW documents contained water-sampling data (Table C-2). CLW documents are publicly available from the Agency for Toxic Substances and Disease Registry (CD accompanying Maslia et al. [2007]). They are indexed by the first page number of a file; often, specific information abstracted from the files by the committee came from later pages in files. The committee reviewed at least one CLW for each sample listed in the table, even if sample information was summarized in multiple CLWs. For each sample, the committee reviewed at least the primary CLW, defined as the original laboratory report of the water-sample analysis results. If the committee looked at other CLWs in addition to the primary laboratory report, they are listed in the "Secondary CLW" column. Additional review was most commonly needed to determine the field sampling date.

Tables C-3 and C-4 summarize all samples abstracted by the committee for the Hadnot Point water-supply system. The universe of possible samples was restricted to those taken in the period from the earliest known water-sampling date in October 1980 through February 7, 1985. Because of removal of contaminated wells from the water-supply system, the committee believes that February 7, 1985, is the last date when samples were taken that would potentially reflect the contaminated water supply. All later samples were believed to have been taken after any measurable residual contamination would have remained in the water-supply system. Results of measurements in distinct samples were included in the table for each unique laboratory report. (See additional comments on this topic below.) There is a separate table of analytic results from mixed water samples taken from the water-distribution system (either before or after treatment; Table C-3) and a table of results from potable-water well samples (Table C-4). The two tables record concentrations of trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, 1,1,1-trichloroethane (TCA), 1,1-dichloroethylene (1,1-DCE), *trans*-1,2-dichloroethylene (1,2-DCE; this compound was assumed if only "DCE" was listed in primary or secondary CLWs), methylene chloride (MC), toluene, and vinyl chloride (VC). Units are micrograms per liter (parts per billion), and the concentrations that appear on the laboratory sheets are recorded directly in the table. "ND" means not detected and appears when it was recorded by the laboratory. Occasionally, a laboratory used other indications for "not detected," such as "<1.0" or "<2.0"; in such cases, these values appear in the table. A dash, "—", appears when the document format suggests that a compound was not analyzed for. When the primary laboratory sheet listed the method detection limit, this value was recorded in the "DL" column of the table. That column was left blank when the information was not explicitly available. Additional sample information is contained in the "sample date" and "sample location" columns. The sample date is intended to be the date on which the sample was collected in the field. Because many of the primary laboratory sheets list the date on which a sample was received by the laboratory, secondary information was needed to make a judgment about the field collection date. This is one example of when "secondary CLWs" were consulted. "Sample location" is a description of the base location where the sample was obtained.

Separate samples were defined on the basis of the presence of a unique laboratory report, so there are distinct entries in the table for samples that were collected at the same location on the same day. The committee does not have information to determine definitively whether those are pure duplicates (one sample split into two vials for laboratory analysis) or separately collected samples. Regardless, measurements on samples collected at the same location on the same day are bound to be more similar than other samples because of their proximity in space and time. In particular, the data include a pair of measurements collected on the same day from well 651. It is unclear from the source documents whether those are measurements on a split sample or measurements on two samples collected on the same day. In addition, there are several instances of multiple samples from the same location in the mixed water samples; in these cases, the sample descriptions have minor distinctions (such as cold-water tap vs hot-water tap or filter 1 vs filter 2) to suggest that the samples were not split.

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TABLE C-3 Concentrations of Contaminants in Hadnot Point Mixed and Finished Water Samples Collected in October 1980–February 7, 1985

		Contaminants, µg/L											
Sample Date	Sample Location	TCE	PCE	1,2-DCE	1,1-DCE	Benzene	MC	TCA	Toluene	VC	DL[a]	Primary CLW[b]	Secondary CLWs[b]
Oct 21,1980	5 locations[c]	D[d]	D[d]	—	—	—	—	—	—	—		0436	
Dec 18, 1980	5 locations[c]	D[d]	D[d]	—	—	—	—	—	—	—		0438	
Jan 29, 1981	5 locations[c]	D[d]	D[d]	—	—	—	—	—	—	—		0441	
Feb 26, 1981	5 locations[c]	D[d]	D[d]	—	—	—	—	—	—	—		0443	
May 27, 1982	NH-1	1,400	15	—	—	—	—	—	—	—		0592	0606
June 1, 1982	Multiple locations	D[d]	D[d]	—	—	—	—	—	—	—		0566	
July 27, 1982	HP WTP raw	19	<1	—	—	—	—	—	—	—		0592	0606
July 27, 1982	Treated water at HP plant	21	<1	—	—	—	—	—	—	—		0592	0606
July 28, 1982	FC-530	—	1	—	—	—	—	—	—	—		0592	0606
Dec 2, 1982	Multiple locations	D[d]	D[d]	—	—	—	—	—	—	—		0694	
Aug 29, 1983	Multiple locations	D[d]	D[d]	—	—	—	—	—	—	—		0952	
Dec 4, 1984	20-raw	46	ND	15	ND	ND	ND	ND	ND	ND	10	5632	1051, 1054, 4546
Dec 4, 1984	20-treated	200	3.9	83	ND	ND	ND	ND	ND	ND	10	5632	1051, 1054, 4546
Dec 10, 1984	HP-treated	2.3	ND	2.3	ND	ND	ND	ND	ND	ND	10	5644	1054, 4546
Dec 13, 1984	20-untreated	ND	ND	ND	ND	ND	54	ND	ND	ND	10	5644	1054, 4546
Dec 14, 1984	HP WTP-raw	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5658	1054, 4546
Dec 15, 1984	HP WTP-raw	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5658	1054, 4546
Dec 16, 1984	HP WTP-raw	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5658	1054, 4546
Dec 17, 1984	HP WTP-raw	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5658	1054, 4546
Dec 18, 1984	HP WTP-raw	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5664	1054, 4546
Dec 19, 1984	20	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5664	1054, 4546
Dec 19, 1984	FC-540	1.2	ND	ND	ND	ND	ND	ND	ND	ND	10	5664	1054, 4546
Jan 29, 1985	670-reservoir	8.2	—	—	—	—	—	—	—	—		1426	4546
Jan 29, 1985	670-treated before reservoir	339.8	—	—	—	—	—	—	—	—		1426	4546
Jan 29, 1985	MOQ PP-2212	1,040.9	—	—	—	—	—	—	—	—		1426	4546
Jan 31, 1985	20-treated	900	—	321.3	—	—	—	—	—	—		4546	5371
Jan 31, 1985	670-bottom	24.1	—	7.4	—	—	—	—	—	—		4546	5371
Jan 31, 1985	670-middle	25.8	—	7.8	—	—	—	—	—	—		4546	5371
Jan 31, 1985	670-top	26.8	—	7.6	—	—	—	—	—	—		4546	5371
Jan 31, 1985	BM-5531	905.5	—	335	—	—	—	—	—	—		4546	5371

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Jan 31, 1985	BM-5677	981.3	—	368.7	—	—	—	—	—	—		4546	5371
Jan 31, 1985	Hydrant MOQ 2204	839.7	—	307.6	—	—	—	—	—	—		4546	5371
Jan 31, 1985	Hydrant tank S830	849	—	340	—	—	—	—	—	—		4546	5371
Jan 31, 1985	MOQ 2212 (cold water)	724.6	—	249.4	—	—	—	—	—	—		4546	5371
Jan 31, 1985	MOQ 2212 (hot water)	612.9	—	201.2	—	—	—	—	—	—		4546	5371
Jan 31, 1985	PP-2600 (fire department)	890.9	—	332.4	—	—	—	—	—	—		4546	5371
Jan 31, 1985	Tank S-2323	407.1	—	159	—	—	—	—	—	—		4546	5371
Jan 31, 1985	Tank SLCH-4004	318.3	—	107.5	—	—	—	—	—	—		4546	5371
Feb 5, 1985	20	429	7.5	150	ND	ND	ND	ND	ND	2.9	10	5509	4708, 4709
Feb 5, 1985	HB filter #1	2.8	ND	ND	ND	ND	ND	ND	ND	ND	10	5509	4708, 4709
Feb 5, 1985	HB filter #2	1.5	ND	ND	ND	ND	ND	ND	ND	ND	10	5509	4708, 4709
Feb 7, 1985	20-filter #1	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	20-filter #2	3.4	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	20-influent	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	20-reservoir finished water	16.8	—	5.3	—	—	—	—	—	—		1426	4546
Feb 7, 1985	5400-Berkley Manor School	135.1	—	44.8	—	—	—	—	—	—		1426	4546
Feb 7, 1985	670-filter #1	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	670-filter #2	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	670-influent	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	670-reservoir finished water	<2.0	—	<2.0	—	—	—	—	—	—		1426	4546
Feb 7, 1985	MOQ 2204, hydrant system	32.4	—	9	—	—	—	—	—	—		1426	4546

[a]Analysis detection limit.
[b]Documents available on CD accompanying Maslia et al. (2007).
[c]Including locations designated as WTP, NH-1, 1202, 65, and FC-530.
[d]Samples were assumed to be detected on the basis of notes on the laboratory reports and inferences from later laboratory reports.
Abbreviations: D = detected, ND = not detected, — = no data available.

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TABLE C-4 Concentrations of Contaminants in Hadnot Point Supply Well Water Samples Collected in October 1980–February 7, 1985

		Contaminants, µg/L										
Sample Date	Supply Well	TCE	PCE	1,2-DCE	1,1-DCE	Benzene	MC	TCA	Toluene	VC	DL[a]	Primary CLW[b]	Secondary CLWs[b]
Dec 4, 1984	601	210	5	88	ND	ND	ND	ND	ND	ND	10	5632	4546
Dec 10, 1984	601	230	4.4	99	ND	ND	10	ND	ND	ND	10	5644	4546
Jan 16, 1985	601	26	ND	8.8	ND	ND	ND	ND	ND	ND	10	5594	4546
Nov 30, 1984	602	1,600	24	630	2.4	120	ND	ND	5.4	18	10	5632	4546
Dec 10, 1984	602	540	ND	380	ND	720	ND	ND	ND	ND	10	5644	4546
Dec 14, 1984	602	340	ND	230	ND	230	ND	ND	12	ND	10	5644	
Feb 4, 1985	602	38	1.5	74	ND	ND	ND	ND	ND	ND	10	5509	4546
Dec 4, 1984	603	4.6	ND	ND	ND	ND	ND	ND	ND	ND	10	5632	4546
Dec 10, 1984	603	ND	ND	ND	ND	ND	7	ND	ND	ND	10	5644	4546
Jan 16, 1985	603	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	606	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Dec 4, 1984	608	110	ND	5.4	ND	3.7	ND	ND	ND	ND	10	5632	4546
Dec 10, 1984	608	13	ND	2.4	ND	4	14	ND	ND	ND	10	5644	4546
Feb 4, 1985	608	9	ND	ND	ND	1.6	ND	ND	ND	ND	10	5509	4546
Jan 16, 1985	609	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Feb 4, 1985	610	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5509	4546
Jan 16, 1985	611	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	613	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	614	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	616	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	620	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	621	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	627	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	632	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	633	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Dec 4, 1984	634	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5632	4546
Dec 10, 1984	634	ND	ND	2.3	ND	ND	130	ND	ND	ND	10	5644	4546
Jan 16, 1985	634	1,300	10	700	ND	ND	ND	ND	ND	6.8	10	5594	4546
Jan 16, 1985	635	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Jan 16, 1985	636	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5594	4546
Dec 4, 1984	637	ND	ND	ND	ND	ND	ND	ND	ND	ND	10	5632	4546
Dec 10, 1984	637	ND	ND	ND	ND	ND	270	ND	ND	ND	10	5644	4546

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Jan 16, 1985	637	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	638	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	640	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	641	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Dec 4, 1984	642	ND	ND	ND	ND	ND	ND	ND	10	5632	4546	
Dec 10, 1984	642	ND	ND	ND	ND	38	ND	ND	10	5644	4546	
Jan 16, 1985	642	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	643	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	644	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	646	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	647	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	648	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	650	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	651	3,200	386	3,400	187	ND	ND	655	10	5594	4546	
Feb 4, 1985[c]	651	18,900	400	7,580	ND	ND	ND	168	200	5509	4546	
Feb 4, 1985[c]	651	17,600	397	8,070	ND	ND	ND	179	200	5509	4546	
Jan 16, 1985	652	9	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	653	5.5	ND	ND	ND	ND	ND	ND	10	5594	4546	
Feb 4, 1985	654	ND	ND	ND	ND	ND	ND	ND	10	5509	4546	
Jan 16, 1985	655	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	639 new	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Jan 16, 1985	639 old	ND	ND	ND	ND	ND	ND	ND	10	5594	4546	
Feb 4, 1985	645-5	ND	ND	ND	ND	ND	ND	ND	10	5509	4546	
Feb 4, 1985	649-3	ND	ND	ND	ND	ND	ND	ND	10	5509	4546	

[a]Analysis detection limit.
[b]Documents available on CD accompanying Maslia et al. (2007).
[c]Water taken from supply well 651 on February 4, 1985, was reported on two laboratory reports; this resulted in two sets of contaminant concentrations. CLW 4546 reports these values in a table as "duplicates."
Abbreviation: ND = not detected.
Source: Maslia et al. 2007.

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TABLE C-5 Positive Detection Summary, Deep Monitoring Wells, Hadnot Point Installation Restoration Sites 78, 6, 9, and 82,[a] Remedial Investigation Sampling Efforts, 1992-1993

				Concentrations (µg/L), Sampling Year and Round[b]		
Well	Depth, ft	Nearest PWS Well	Contaminant	1992	1993 Round 1	1993 Round 2
78-GW04-3	153	608	Benzene	30	Not sampled	Not sampled
			cis-1,2-DCE	3		
			Phenol	5		
			Arsenic	118		
			Cadmium	21		
			Manganese	591		
78-GW09-3	150	608	Alpha chlordane	0.11	Not sampled	Not sampled
			Bis(2-ethylhexyl) phthalate	18		
			Phenol	8		
78-GW24-3	148	634	Benzene	35	Not sampled	Not sampled
			cis-1,2-DCE	3		
			trans-1,2-DCE	1		
			Naphthalene	2		
			Phenol	5		
			Cadmium	5		
78-GW30-3	153	634	[c]	ND	Not sampled	Not sampled
78-GW31-3	153	601	Benzene	15.3	Not sampled	Not sampled
			cis -1,2-DCE	1		
			Phenol	4		
78-GW32-3	153	601, 602, 630	1,2-DCA	1	Not sampled	Not sampled
			2-Methylphenol	2		
			Phenol	2		
			TCE	6		
6-GW01-DW	112.5	651	Benzene		Not sampled	6.7
			Chlorobenzene			13
			Chloromethane			1.4
			1,4-Dichlorobenzene			17
			1,2-DCA			30
			1,1-DCE			51
			trans-1,2-DCE	5,600		26,000
			Ethylbenzene	48		52
			Methylene Chloride	790		
			PCE	630		920
			Phenol	3		
			1,1,2-TCA			5.8
			TCE	58,000		50,000
			Toluene			1.4

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				Vinyl chloride		800
				Xylenes		2.1
				Barium	71.5	
				Manganese	21.6	
6-GW01-DA	230	651	TCE base/top	Not sampled	83/160	Not sampled
			Total 1,2-DCE base/top		38/100	
			PCE base/top		1.3/2.9	
6-GW02-DW	119	651	Phenol	3	Not sampled	ND
			TCE	1.4		
			Arsenic	3.8		
6-GW07-DW	100.5	651	1,1-DCE	0.6	Not sampled	
			Phenol	3		
			TCE	1.2		2.1
			Aluminum	336		
			Manganese	33.5		
6-GW15-DW	155	651	TCE	Not sampled	34	Not sampled
			Total 1,2-DCE		9.1	
			PCE		1	
6-GW27-DW	110	651	Bis(2-ethylhexyl)phthalate	5	Not sampled	
			Chlorobenzene			3.6
			1,2-DCA			16
			1,1-DCE			55
			trans-1,2-DCE	5,800		30,000
			PCE			18
			Phenol	22		
			TCE	18,000		22,000
			Vinyl chloride			250
			Antimony	15.3		
			Manganese	14.2		
6-GW28-DW	114.5	651	Bis(2-ethylhexyl)phthalate	22	Not sampled	
			Chlorobenzene			18
			1,2-DCA			7.5
			1,1-DCE			12
			trans-1,2-DCE	500		5,800
			Ethylbenzene			2
			PCE			42
			Phenol	2		
			TCE	3,600		9,100
			Vinyl chloride			100
			Manganese	14.2		

(Continued)

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TABLE C-5 Continued

Well	Depth, ft	Nearest PWS Well	Contaminant	Concentrations (µg/L), Sampling Year and Round[b]		
				1992	1993 Round 1	1993 Round 2
6-GW36-DW	95	651	TCE	Not sampled	6.4	Not sampled
			Total 1,2-DCE		3.4	
6-GW37-DW	95	651	TCE	Not sampled	60	Not sampled
			Total 1,2-DCE		120	
			1,2-Dichlorobenzene		2.6	
9-GW07-DW	110	635	Bis(2-ethylhexyl)phthalate	2	62	
			Dimethyl phthalate	1		
			Phenol	7	5	
			TCE			1.2
			Aluminum	207	1,360	
			Barium	34.9	356	
			Manganese	14.8	49.3	
			Selenium		2.1	

[a]Monitoring wells for site 82 are labeled "6"; sites 6 and 82 are adjacent.
[b]Data for this table copied from tables in remedial investigation reports. Blanks appear as in original tables. The committee interprets blanks as representing analyses that registered "below the detection limit."
[c]None of the chemicals test for were detected.
Abbreviation: ND = not detected.
Note: Data abstracted from Remedial Investigation Report, Operable Unit 1, sites 21, 24, and 78, Marine Corps Base, Camp Lejeune, NC, Undated Report. Tables 4-6 (Organic Chemicals) and 4-7 (TAL Total Metals and Cyanide).
Data abstracted from Remedial Investigation Report, Operable Unit 2, sites 6, 9, and 82, Marine Corps Base, Camp Lejeune, NC, Contract Task Order 0133, prepared by Baker Environmental, August 20, 1993.
Depths: Tables 1-1, 2-8, 2-9, 2-18, and 2-21.
Concentrations: Chapter 4 and Tables 4-5 (Phase I Organic Chemicals) and 4-6 (Phase I TAL Total Metals and Cyanide).
Tables 4-23 (Phase II Round 1 Organic Chemicals), 4-24 (Phase II Round 1 TAL Total Metals and Cyanide), and 4-10 (Comparison of Organic Chemicals, Round I and Round II).

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TABLE C-6 Estimated Number of Residences by Water-Treatment Plant, 1941-2000

Water Treatment Plant and Distribution System	Years of Operation	Housing Areas
Courthouse Bay water system	1942-2000	Courthouse Bay housing—8 homes
		Courthouse Bay barracks
Camp Johnson water system	1941-1946	Camp Johnson barracks
Camp Geiger water system	1941-1976	Camp Geiger barracks
Rifle range water system	1942-1993	Rifle range housing—5 homes
		Rifle range barracks
Onslow County water system	1994-2000	Rifle range housing—5 homes
		Rifle range barracks
Hadnot Point water system	1943-1971	Midway Park housing—699 homes
		Paradise Point general officer housing—4 homes
		Paradise Point two-story housing—216 homes
	1947-1971 Added	Hospital Point housing—24 homes
		Paradise Point cracker box housing—100 homes
	1948-1971 Added	Paradise Point Cape Cod housing—67 homes
	1961-1971 Added	Berkeley Manor housing—677 homes
	1962-1971 Added	Paradise Point Capehart housing—123 homes
Hadnot Point water system	1943-2000	French Creek barracks
		Hadnot Point barracks
Tarawa Terrace water system	1952 - 1986	Tarawa Terrace I & II housing—1,843 homes
		Knox trailer park—112 spaces
Marine Corps Air Station water system	1958 - 2000	Marine Corps Air Station housing—435 homes
	1977-2000 Added	Camp Geiger barracks
Holcomb Boulevard water system	1972-2000	Midway Park housing—699 homes
		Paradise Point general officer housing—4 homes
		Paradise Point two-story housing—216 homes
		Paradise Point cracker box housing—100 homes
		Paradise Point Cape Cod housing—67 homes
		Berkeley Manor housing—677 homes
		Paradise Point Capehart housing—123 homes
	1978-2000 Added	Watkins Village housing—250 homes
	1987-2000 Added	Tarawa Terrace I & II housing—1,843 homes
		Knox trailer park—112 spaces
		Camp Johnson barracks
	1989-2000 Added	Knox trailer park expanded by—75 spaces

Source: U.S. Marine Corps.

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Appendix D

Review of Other Chemical Contaminants of Concern

Chapter 2 identified seven contaminants of the water supply at Camp Lejeune that the committee judged as warranting further attention in addition to trichloroethylene and perchloroethylene: 1,2-dichloroethylene (1,2-DCE; *cis*- and *trans*-forms), 1,1-dichloroethylene (1, 1-DCE), benzene, methylene chloride (MC), toluene, and vinyl chloride (VC). (Information about the detection of these chemicals is presented in Chapter 2 and Appendix C.) The committee used comprehensive reviews performed by other organizations and agencies to compile the following overview of the potential health effects of those contaminants.

1,2-DICHLOROETHYLENE

The health effects of 1,2-DCE were reviewed by ATSDR (1996). 1,2-DCE is used to produce solvents and in chemical mixtures. There are two forms (isomers) of 1,2-DCE: *cis*-1,2-DCE, and *trans*-1,2-DCE. The two forms are sometimes present as a mixture. 1,2-DCE evaporates rapidly into air. Most 1,2-DCE in the soil surface or bodies of water will evaporate into air, and it can travel through soil or dissolve in water in soil. It is possible that it can contaminate groundwater. There is a slight chance that 1,2-DCE will break down into VC, which is believed to be more toxic than 1,2-DCE. One can be exposed by breathing 1,2-DCE that has leaked from hazardous-waste sites and landfills; by drinking contaminated tap water or breathing vapors from contaminated water while cooking, bathing, or washing dishes; by breathing it; by touching it; or by touching contaminated materials in the workplace. The most important effects of 1,2-DCE exposure are hematologic (such as a decrease in the number of red blood cells) and hepatic. Clinical symptoms that have been reported in humans exposed to 1,2-DCE at high concentration in air include nausea, drowsiness, fatigue, intracranial pressure, and ocular irritation. One fatality has been reported. No information is available on oral toxicity of 1,2-DCE in humans. No information is available on the relative toxicities of *cis*- and *trans*-1,2-DCE in humans. A variety of genotoxicity tests have been performed on 1,2-DCE. The predominant results are negative, and no carcinogenicity studies were found in the literature. EPA has determined that *cis*-1,2-DCE is not classifiable as to human carcinogenicity. No EPA cancer classification of *trans*-1,2-DCE is available. Specific effects of 1,2-DCE in animals are discussed below.

Hepatic Toxicity

Subchronic exposure to *trans*-1,2-DCE in drinking water (17-452 mg/kg per day) has caused biochemical changes in the livers of mice (Barnes et al. 1985). Both sexes had increased glucose concentrations, and females had decreased serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic

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transaminase, and aniline hydroxylase activity at all doses. Males had significantly decreased glutathione at the highest dose. In studies with rats, increased relative hepatic weights were observed with *cis*-1,2-DCE at 32 mg/kg per day and higher (McCauley et al. 1995). Variable changes in hepatic enzyme concentrations were seen, but no histopathologic lesions of the liver. A study of *trans*-1,2-DCE administered to rats in microcapsules for 14 weeks reported increased hepatic weights in females but not males at 395 mg/kg per day (NTP 2002c). No significant alterations in clinical-chemistry measures were found.

In an inhalation study, fatty degeneration of liver lobules was observed in female rats exposed to *trans*-1,2-DCE at 200 ppm for 8 or 16 weeks (Freundt et al. 1977).

Renal Toxicity

There is little clinical or histologic evidence of renal toxicity in experimental studies of 1,2-DCE (ATSDR 1996). A recent 14-week study of *trans*-1,2-DCE reported significantly reduced absolute renal weights in male rats at 1,540 mg/kg per day (NTP 2002c) but no gross or microscopic lesions.

Pulmonary Toxicity

With the exception of some effects on the lungs after lethal doses of *trans*-1,2-DCE, experimental studies of DCE isomers have yielded little clinical or histologic evidence of pulmonary toxicity (ATSDR 1996).

Reproductive Toxicity

One study of pregnant rats exposed by inhalation to *trans*-1,2-DCE at 6,000 or 12,000 ppm found a significant increase in the mean number of resorptions per litter (Hurtt et al. 1993), but the authors noted that the value was within the range of historical control values; maternal toxicity was observed. The National Toxicology Program (NTP 2002c) reported no significant changes in sperm motility or vaginal cytology in rats or mice fed microencapsulated *trans*-1,2-DCE at doses as high as 8,065 mg/kg per day for 14 weeks.

Developmental Toxicity

Hurtt et al. (1993) reported significantly reduced mean combined and female fetal weights in rats exposed to *trans*-1,2-DCE by inhalation during pregnancy at 12,000 ppm. The dams had frank maternal toxicity, as evidenced by reduced food consumption and reduced weight gain.

Neurotoxicity

Several studies have reported central nervous system (CNS) depression in rats after exposure to *cis*-1,2-DCE at 878 mg/kg per day (McCauley et al. 1995) or to either isomer of 1,2-DCE at lethal doses (Barnes et al. 1985; McCauley et al. 1995). After inhalation exposure, experimental animals have exhibited lethargy, behavioral changes, and other neurologic effects (ATSDR 1996), but the significance of the changes is unclear. A functional observational battery performed on mice and rats given microencapsulated *trans*-1,2-DCE in their feed at up to 8,065 mg/kg per day for 14 weeks found no evidence of CNS depression (NTP 2002c).

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Immunotoxicity

In studies of mice given *trans*-1,2-DCE orally at 224 mg/kg per day, an increase in leukocyte counts and a decrease in relative thymus weight were found in females, but no changes in cell-mediated or humoral immunity were observed (Barnes et al. 1985; Shopp et al. 1985). However, in one study, male mice treated with *trans*-1,2-DCE at 17-387 mg/kg per day exhibited decreased spleen-cell production of antibody against sheep erythrocytes, which did not result in a functional effect on the humoral immune system (Shopp et al. 1985). An inhalation-exposure study of *trans*-1,2-DCE by Freundt et al. (1977) reported fatty degeneration of Kupffer cells, decreased leukocyte counts, and pulmonary infiltration at 200 ppm and greater.

Hematopoietic Toxicity

Female rats exposed to *cis*-1,2-DCE exhibited decreased hemoglobin concentrations, red blood cell counts, and hematocrit values at 98 mg/kg per day for 90 days (McCauley et al. 1995) but not at lower doses, and no statistically significant effects were observed in male rats. Other studies have reported no hematologic effects in rats or mice after oral exposure to *trans*-1,2-DCE at up to 3,114 mg/kg per day for 90 days (Barnes et al. 1985; Hayes et al. 1987).

In a more recent 14-week study, the NTP (2002c) reported mild decreases in hematocrit values, hemoglobin concentrations, and red blood cell counts in rats fed microcapsules containing *trans*-1,2-DCE at 380 mg/kg per day for males and 1,580 mg/kg per day for females. Mice similarly exposed did not have those changes.

Genotoxicity

Genotoxicity studies of 1,2-DCE have had predominantly negative results (ATSDR 1996; NTP 2002c). Both isomers were negative in mutagenicity assays with bacteria and chromosomal-aberration tests with Chinese hamster cells. Mixed results have been reported with respect to chromosomal effects in mammalian systems (ATSDR 1996; NTP 2002c). Negative results were reported in a peripheral-blood micronucleus test performed with mice fed microencapsulated *trans*-1,2-DCE for 14 weeks (NTP 2002c).

Cancer

No cancer bioassays of either isomer of 1,2-DCE have been performed.

1,1-DICHLOROETHYLENE

The health effects of 1,1-DCE, also known as vinylidene chloride, were reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR 1994), the International Agency for Research on Cancer (IARC 1999a), and the U.S. Environment Protection Agency (EPA 2002). 1,1-DCE is an industrial chemical not found naturally in the environment. It is used to make plastics (such as flexible films for wrapping food and packaging materials), to make flame-retardant coatings for fiber and carpet backings, and in piping, coating for steel pipes, and adhesives. 1,1-DCE evaporates quickly from water and soil, breaks down slowly in water, and is slowly transformed to other, less harmful chemicals in soil. One may be exposed to 1,1-DCE through employment in industries that make or use 1,1-DCE, through food that is wrapped in plastic that contains 1,1-DCE, through drinking water from the small percentage of supplies that contain 1,1-DCE, and through air near factories or hazardous-waste sites. It has been used in the past

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as a gaseous anesthetic agent; its use as an anesthetic agent was discontinued after it was discovered that it induced cardiac arrhythmia at anesthetic doses. Inhalation of high concentrations of 1,1-DCE is known to cause reversible nervous system impairment. Workers exposed to 1,1-DCE have reported a loss in hepatic function, but other chemicals were present. Specific effects of 1,1-DCE in animals are discussed briefly below.

Hepatic Toxicity

Acute doses of 1,1-DCE administered orally to rats at 25-100 mg/kg per day induced hepatic toxicity, including alterations in hepatic enzymes indicative of damage or dysfunction and histopathologic evidence of damage (ATSDR 1994). Gavage studies of more prolonged exposure to 1,1-DCE (13 weeks) reported hepatic necrosis in male mice exposed at 250 mg/kg per day and in female mice at 5 mg/kg per day (NTP 1982). Similarly exposed rats had chronic hepatic inflammation at a dose of 250 mg/kg per day. Drinking-water and feed studies have reported little or milder evidence of hepatic toxicity. For example, Quast et al. (1983) reported no histopathologic changes in the livers of dogs exposed to 1,1-DCE in drinking water at 25 mg/kg per day for 97 days. In 2-year exposure studies with rats, only mild hepatocellular changes were observed at doses of 6-30 mg/kg per day (Rampy et al. 1977; Quast et al. 1983).

Inhalation-exposure studies have reported similar evidence of hepatic toxicity in rats and mice (ATSDR 1994). After some of the longer exposures, changes observed at 25 ppm included cytoplasmic vacuolation (ATSDR 1994) and fatty infiltration of the liver (Quast et al. 1986), and at 125 ppm, centrilobular fatty degeneration and hepatic necrosis (ATSDR 1994). Food intake appears to affect the hepatic toxicity of 1,1-DCE: greater effects have been observed in fasted rats in both oral and inhalation studies (ATSDR 1994).

Renal Toxicity

Several types of renal effect have been reported in experimental animals exposed to 1,1-DCE orally and by inhalation. For example, single oral doses of 1,1-DCE at 200 mg/kg or greater caused histopathologic changes in the kidneys of rats (ATSDR 1994). However, no renal effects were observed in experimental animals exposed at 30 mg/kg per day or less in chronic-exposure studies (Rampy et al. 1977; Quast et al. 1983).

In acute-inhalation studies, renal effects have included enzyme changes, hemoglobinuria, increased kidney weight, and tubular swelling, degeneration, and necrosis at concentrations as low as 50 ppm in rats and 10 ppm in mice (ATSDR 1994). In toxicity studies of longer duration (52 weeks), severe renal effects have been observed in mice at 10-25 ppm (Maltoni et al. 1985) but not in rats (Maltoni et al. 1985; Quast et al. 1986).

The renal toxicity of 1,1-DCE appears to be related to sex-specific expression of CYP2E1 in male mice (EPA 2002). One proposed mechanism of renal toxicity is the formation of cytotoxic intermediates from CYP2E1 activity in the kidneys. Another possible mechanism is the formation of *S*-conjugates that are metabolized by β-lyase in the proximal renal tubules and yield products that interact with macromolecules (ATSDR 1994; EPA 2002).

Pulmonary Toxicity

Acute inhalation exposure to 1,1-DCE has produced swelling, edema, and congestion of the lungs of rodents at 500-15,000 ppm and in some species at concentrations as low as 20 ppm (ATSDR 1994). One acute oral study of 1,1-DCE (100 mg/kg) found pulmonary injury in mice (Forkert and Reynolds 1982). Clara cells are especially targeted in the lungs of mice (Forkert et al. 1986). In longer-term inhala-

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tion-exposure studies, no histopathologic changes in the lungs or respiratory system were observed in several test species at 100 ppm (Prendergast et al. 1967; Quast et al. 1986).

Reproductive Toxicity

No evidence of reproductive toxicity was found in a three-generation study of rats exposed to 1,1-DCE in drinking water at up to 200 ppm (Nitschke et al. 1983). Similarly, no effects were found in reproductive studies in male rats exposed to 1,1-DCE by inhalation at up to 50 ppm (Anderson et al. 1977; ATSDR 1994).

Developmental Toxicity

Murray et al. (1979) studied the effects of inhaled 1,1-DCE on pregnant rats. Maternal and embryo toxicity was observed in rats exposed during gestation at 80 ppm or greater and in rabbits at 160 ppm, but there was no evidence of teratogenicity in either species. A study of 1,1-DCE administered in the drinking water of pregnant rats at 200 ppm found no evidence of maternal or fetal toxicity or teratogenicity (Murray et al. 1979).

In another study, 1,1-DCE was administered to rats in drinking water before mating and/or during gestation (Dawson et al. 1993). A significant increase in congenital cardiac malformations was observed in the fetuses of rats treated before mating and during gestation at a drinking-water concentration of 0.15 or 100 ppm, but a dose-response relationship was not demonstrated. However, a three-generation study of rats exposed to 1,1-DCE in drinking water at up to 200 ppm did not find cardiac changes (Nitschke et al. 1983). One study reported a significant increase in the mean number of mouse fetuses with an unossified incus and with incompletely ossified sternebrae at a drinking-water concentration of 15 ppm (EPA 2002). Other evidence of developmental toxicity was observed at higher concentrations, but frank maternal toxicity was also observed at those concentrations.

Neurotoxicity

Like other organic solvents, 1,1-DCE at high concentrations has a narcotic effect on experimental animals (ATSDR 1994). In general toxicology studies, there have been no reports of neurologic effects of 1,1-DCE after oral or inhalation exposure, but these studies were not designed specifically to evaluate neurologic effects.

Immunotoxicity

Ban et al. (2003) exposed mice to 1,1-DCE by inhalation at 5-15 ppm and tested systemic and local immune response. IgM response in the lymph nodes to challenge with sheep red blood cells was increased, and the highest exposure provoked a similar response in the spleen. A significant increase in the release of interferon-gamma was found in lymph node cultures but the increase in spleen cell cultures was smaller. The investigators concluded that lung-associated lymph nodes could be sensitive targets for inhaled 1,1-DCE.

Hematopoietic Toxicity

No significant hematologic changes have been reported in drinking-water studies of 1,1-DCE in

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dogs exposed at 25 mg/kg per day for 97 days (Quast et al. 1983) or in rats exposed at 30 mg/kg per day for 2 years (Rampy et al. 1977; Quast et al. 1983). No evidence of hematotoxicity was observed in inhalation studies with rats and mice exposed at 55-75 ppm for 1 year or more (Lee et al. 1977; Quast et al. 1986).

Genotoxicity

1,1-DCE has been shown to be mutagenic, to induce chromosomal aberrations and sister-chromatid exchanges in vitro, and to cause DNA damage in vivo (ATSDR 1994; EPA 2002). In most cases, metabolic activation was required to produce the results.

Cancer

A number of chronic bioassays of oral and inhaled 1,1-DCE have been performed in rodents (ATSDR 1994; EPA 2002; Roberts et al. 2002). Only one inhalation study has shown evidence of carcinogenicity (Maltoni et al. 1985); male mice exposed at 25 ppm had an increased incidence of renal adenocarcinomas. IARC judges 1,1-DCE as not classifiable with respect to human carcinogenicity (IARC 1987, 1999a).

BENZENE

Benzene, also known as benzol, has industrial and natural sources. First discovered and isolated from coal tar in the 1800s, benzene is made mostly from petroleum today and ranks in the top 20 in production volume among chemicals produced in the United States. Other sources of benzene include gas emissions from volcanoes, forest fires, gasoline, and cigarette smoke. Benzene is widely distributed in the environment, and low-level inhalation over long periods is of most concern. People employed in industries that make or use benzene or products that contain it are probably exposed to the highest concentrations of atmospheric benzene. People with benzene-contaminated tap water can be exposed from drinking the water or eating foods prepared with it; by inhalation during showering, bathing, and cooking; and through dermal contact during showering and bathing.

Benzene is a well-studied chemical and has been the subject of several comprehensive reviews and risk assessments (IARC 1982, 1987; EPA 1998b, 2002; ATSDR 2007). It is well established in those reviews that benzene is associated with effects on the hematologic, immune, and nervous systems. Evidence of the effects is found in reports of controlled animal experiments (Gill et al. 1980; Rozen et al. 1984; Cronkite et al. 1985, 1989; Rosenthal and Snyder 1985; Molnar et al. 1986) and in the epidemiologic literature, especially reports of occupational studies of benzene exposure (Srbova et al. 1950; Yin et al. 1987a; Kraut et al. 1988; Rothman et al. 1996; Lan et al. 2004).

There is agreement in the scientific community that benzene is a human carcinogen (IARC 1987; EPA 1998b; NTP 2005; ATSDR 2007). Inhalation studies of rodents show that benzene causes cancer in multiple tissues, and there is strong evidence of lymphoid tumors in mice (Snyder et al. 1980, 1984, 1988; Cronkite et al. 1984, 1985, 1989; Maltoni et al. 1989; Farris et al. 1993). Acute myelogenous leukemia is the predominant cancer found in humans exposed to benzene and has been documented in studies of workers exposed to benzene in rubber hydrochloride manufacturing plants (Rinsky et al. 1981, 1987) and in factories in China (Yin et al. 1987b, 1989, 1996; Hayes et al. 1996, 1997). Most epidemiologic studies have also found an increased risk of leukemia in general, total lymphatic and hematopoietic cancers, and other specific types of leukemia, such as chronic lymphocytic leukemia (Savitz and Andrews 1997; NTP 2005). The health effects of benzene were most recently reviewed by ATSDR (2007). The central conclusions of that review are summarized below.

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The carcinogenicity of benzene in exposed workers is well documented. Epidemiologic studies of occupational cohorts provide clear evidence of a causal relationship between occupational exposure to benzene and benzene-containing solvents and acute myelogenous leukemia. All leukemias and myelodysplastic syndromes have been linked to occupational exposure to benzene at high concentrations, and there appears to be a dose-response relationship. Other cancer outcomes associated with occupational exposure to benzene in some studies are non-Hodgkin lymphoma and multiple myeloma; however, these associations have not been consistently observed among studies.

Benzene has been shown to have adverse hematologic and immunologic effects. All the major types of blood cells are susceptible (erythrocytes, leukocytes, and platelets). Severe toxicity may result in hypercellular bone marrow that exhibits ineffective hematopoiesis and pancytopenia (reduced numbers of all types of blood cells). Severe damage to the bone marrow involving cellular aplasia is known as aplastic anemia and can lead to leukemia. Early studies of benzene-exposed workers demonstrated that chronic exposure to benzene at air concentrations of 10 ppm or more had adverse hematologic effects, which increased in severity with increasing benzene concentration. More recent epidemiologic studies have observed hematologic effects (including significant reductions in the numbers of various types of blood cells) in workers chronically exposed to benzene at less than 10 ppm and even at 1 ppm or less. After inhalation exposure for intermediate and chronic durations, benzene has had adverse immunologic effects, including decreases in concentrations of antibodies and leukocytes in benzene-exposed workers.

The current literature suggests that humans exposed to benzene in an occupational setting for acute, intermediate, or chronic durations by inhalation and orally are at risk for neurologic effects. However, benzene concentrations in ambient air, in drinking water, and at hazardous-waste sites are lower and not likely to be of concern. Limited information is available on other systemic effects in humans and is associated with high exposure. Respiratory effects, dermal effects (skin irritation and burns), ocular effects (irritation), and cardiovascular effects (particularly ventricular fibrillation) have been suggested after exposure to benzene vapors. Gastrointestinal effects have been noted after fatal inhalation exposure (congestive gastritis) or ingestion (toxic gastritis and pyloric stenosis). Reports of renal effects refer to renal congestion after fatal inhalation exposure.

The evidence of effects of benzene exposure on human reproduction is not sufficient to demonstrate a causal association. Epidemiologic studies implicating benzene as a developmental toxicant have many limitations, and it is not possible to assess the effect of benzene on the human fetus.

METHYLENE CHLORIDE

MC is used in various industrial processes, including paint stripping, pharmaceutical manufacturing, paint-remover manufacturing, and metal cleaning and degreasing. It may also be found in some aerosol and pesticide products and is used in the manufacture of photographic film. MC is a toxic chemical that is known to cause death in humans at high doses (ATSDR 2000a). Human fatalities are most often associated with effects on the nervous system. In general, people can be exposed through air, water, food, or such products as paint thinner (ATSDR 2000a). ATSDR (2000a) reviewed the scientific literature for toxicologic profile. The Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency also reviewed the available studies to develop a public-health goal for MC in drinking water (CalEPA 2000b).

In addition, three organizations reviewed the scientific literature to determine whether MC causes cancer. The NTP concluded that MC is "reasonably anticipated" to be a human carcinogen on the basis of evidence of carcinogenicity in mice. In 1999, IARC concluded that MC was "possibly carcinogenic to humans." In 1991, EPA classified it as a "probable human carcinogen" on the basis of sufficient evidence of hepatic and lung cancer and mammary tumors in experimental animals (EPA 1991). EPA announced that it had begun a reassessment of MC, but no findings have been posted.

In 1992, EPA adopted a maximum contaminant level (MCL) in drinking water of 5 ppb and an MCL goal of 0 ppb, citing concerns about hepatic effects and cancer (EPA 2003). The MCLs reflected

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consideration of the potential for health effects and of the feasibility and cost of treatment technologies and so may not represent health-based standards. California adopted a public-health goal in drinking water of 4 ppb on the basis solely of health concerns. The California drinking-water standard, like the federal standard, is 5 ppb and was adopted in 1994 (CalEPA 2000b).

IOM (2003) reviewed the human health effects of chronic exposure to MC, including results of several occupational studies, such as those of aircraft-maintenance workers (Blair et al. 1998), cellulose-fiber production-plant workers (Lanes et al. 1993; Gibbs et al. 1996), photographic-film base-manufacturing workers (Hearne and Pifer 1999), cellulose triacetate film workers (Tomenson et al. 1997), and lamp-manufacturing workers (Shannon et al. 1988). No consistent pattern of increased risk of any health effect was found. The present committee performed an updated literature review to identify new studies since the IOM (2003) review. No new studies in which exposure to MC could be specifically evaluated were found. IOM concluded that there was inadequate/insufficient evidence to determine whether there is an association between MC and cancer or neurologic, reproductive, developmental, or other health effects. The committee supports IOM's conclusions.

We also surveyed reports published since the earlier reviews were performed. Little testing has been done for additional health end points. Most of the published research focuses on the interpretation of data from studies in animals and addresses such issues as differences between mice and humans (e.g., Jonsson and Johanson 2001; Sherratt et al. 2002; Slikker et al. 2004), development of physiologically based pharmacokinetic models (e.g., Sweeney et al. 2004), and application of findings to cancer risk assessment (e.g., David et al. 2006; Marino et al. 2006; Starr et al. 2006). One study reported that ingestion of acetaminophen, a commonly used analgesic, increased the activation of MC in rats (Kim et al. 2007). With regard to additional studies of end points of concern, the committee found one new investigation of the immunotoxicity of MC, which is discussed below.

Hepatic Toxicity

Studies of animals exposed to MC in drinking water have reported effects on the liver. Kirschman et al. (1986) reported changes in hepatic cells (including centrilobular necrosis, granulomatous foci, and cytoplasmic eosinophilic bodies) in male rats after 90 days of exposure to MC in drinking water at 1,200 mg/kg per day. Less serious effects were observed at the lowest dose, 166 mg/kg per day, in males and a slightly higher dose in females. MC was reported to alter the distribution of lipids among tissues. The study also reported changes in blood chemistry characteristics, such as fasting glucose, cholesterol, and triglyceride values, at all doses, at 1 and 3 mo. The same authors reported subtle centrilobular fatty changes in male $B6C3F_1$ mice exposed for 90 days at 587 mg/kg per day.

Serota et al. (1986a,b) reported hepatic changes, including cellular alterations in Fischer rats exposed to MC for 78-104 weeks at 55 mg/kg per day and increased hepatic fat in $B6C3F_1$ mice exposed for 2 years at 236 mg/kg per day.

EPA reported a NOAEL of 5.8 and 6.5 mg/kg per day for histologic alterations of the liver in male and female rats, respectively, exposed during a 2-year bioassay of exposure in drinking water (EPA 1988). The lowest observed-adverse-effects levels (LOAELs) reported were 52.6 and 58 mg/kg per day in male and female rats, respectively (National Coffee Association [1982], as cited by EPA 1988). EPA used those values to set a reference dose for exposure in drinking water of 0.06 mg/kg per day. EPA has not set a reference dose for inhalation exposure.

Kjellstrand et al. (1986) reported increased hepatic weight in mice exposed at 75 ppm for 90 days. No NOAEL was reported. Burek et al. (1984) reported hepatocellular vacuolization and multinucleated hepatocytes in Sprague-Dawley rats after exposure at 500 ppm for 2 years 5 days/week and 6 h/day but did not report a NOAEL. Nitschke et al. (1988a,b) reported multinucleated hepatocytes in females of the same species after inhalation exposure at 200 ppm for the same duration, with a NOAEL of 50 ppm. Those data were used by ATSDR to derive a chronic inhalation minimal risk level of 0.3 ppm. In 2-year MC bioassays with rats, hepatocellular vacuolization and multinucleate hepatocytes were found at a con-

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centration of 500 ppm (NTP 1986d; Nitschke et al. 1988a). NTP (1986d) also reported hepatic hemosiderosis, cytomegaly, necrosis, granulomatous inflammation, and bile duct fibrosis.

Reproductive Toxicity

The NTP (1986d) exposed mice and rats to MC by inhalation at up to 1,500 ppm for 2 years. Mice exhibited atrophy of the uterus, ovary, and testes. In a dominant lethal study, no microscopic effects on the testes were found in mice exposed to MC at vapor concentrations up to 200 ppm (Raje et al. 1988). In a two-generation reproductive-toxicity study, no effects on fertility, litter size, neonatal growth, or survival were found in rats exposed by inhalation at up to 1,500 ppm (Nitschke et al. 1988a).

Developmental Toxicity

Schwetz et al. (1975) reported an extra ossification in the sternum or delayed ossification of sternebrae in rats and mice exposed to MC by inhalation at 1,250 ppm. An increased incidence of dilated renal pelvis was also observed in rats. In another study, no teratogenic effects were reported after rats were exposed at 4,500 ppm before mating or during gestation (Hardin and Manson 1980), but a followup study of the offspring found alterations in rates of behavioral habituation to novel environments. Several other studies of exposure to MC during reproduction or development found no significant effects on survival, viability, growth, or development (ATSDR 2000a).

Neurotoxicity

Two studies reported neurologic effects. Briving et al. (1986b) reported alterations in the amino acids present in the brain in gerbils exposed by inhalation at 210 ppm for 3 mo. Rosengren et al. (1986b) reported decreased DNA concentrations in the hippocampus in Mongolian gerbils exposed by inhalation at 210 ppm for 7-16 weeks. Negative findings in some neurologic tests in rats after exposure at 2,000 ppm for 13 weeks have been reported (Mattsson et al. 1990).

Immunotoxicity

One study has looked at immune system effects. Warbrick et al. (2003) exposed Sprague-Dawley rats to MC by inhalation at 5,000 ppm by inhalation for 6 h/day 5 days/week for 28 days. Immune response was evaluated by the capacity of the rats to mount an antibody response to sheep red blood cells. The study reported that relative spleen weight was reduced in females but not in males. The authors reported no significant differences in antibody production between treated rats and controls.

Hematologic Effects

MC can contribute to an increase in concentrations of carbon monoxide in the blood, as first documented in a 1993 case report (ATSDR 2000a). That can cause hypoxia. Recent results suggest that the effect can be enhanced by coexposure to acetaminophen, a widely used medication (Kim et al. 2007). The significance of the report for chronic exposure does not appear to have been assessed. Similar effects may be of concern in connection with other solvents that are metabolized through pathways similar to that of MC, including others included in this report. The issue may warrant additional attention.

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Genotoxicity

Mixed results have been found in genotoxicity assays of MC. In vitro studies with human cells have reported that MC induced sister-chromatid exchanges, chromosomal breaks, and chromosomal loss, but studies with rodent cells have not. Single-strand breaks in DNA have been observed in studies with mammalian cells, but there has been no evidence of mutations (IARC 1999b). There is some evidence of tissue-specific genotoxic effects (Sasaki et al. 1998), which could be related to the differential expression of metabolizing enzymes.

Cancer

Three studies reported cancer in experimental animals after inhalation exposure. Mennear et al. (1988) exposed Fischer 344 rats to MC at 1,000-4,000 ppm 6 h/day 5 days/week for 102 weeks and reported an increase in mammary tumors in males at 4,000 ppm and in females at all doses. The NTP (1986d) reported the same results. That strain of rat is known to have a high background incidence of tumors. Nitschke et al. (1988b) exposed rats at lower doses (0, 50, 200, and 500 ppm) in another 2-year study and reported increases in numbers of tumors per animal in females in the 500-ppm group; no effects were reported in males.

Mennear et al. (1988) exposed $B6C3F_1$ mice to MC at 2,000 or 4,000 ppm 6 h/day 5 days/week for 102 weeks and reported increases in hepatic and lung tumors in mice exposed at 2,000 ppm or higher. The NTP (1986d) reported the same result.

Maltoni et al. (1988b) reported a statistically significant increase in pulmonary tumors in male mice treated with MC by gavage at 500 mg/kg per day for 64 weeks. Supporting evidence of lung-tumor development in mice after inhalation exposure to MC is found in studies by Kari et al. (1993) and Maronpot et al. (1995).

A 2-year drinking-water study with MC up to 250 mg/kg per day found an increase in the incidence of combined hepatocellular carcinomas and neoplastic nodules in female rats and male mice compared with concurrent controls (Serota et al. 1986a,b). However, the incidence was within the range for historical controls, and there was no dose-response relationship.

Other Effects

Other effects of MC reported in experimental animal studies include alterations in urinary pH and renal weights in rats and renal tubular changes in dogs, rats, and mice after inhalation exposure (ATSDR 2000a; CalEPA 2000b).

TOLUENE

The health effects of toluene have recently been reviewed by ATSDR (2000b). This section will first summarize the central conclusions of the ATSDR review pertaining to human studies and then summarize the toxicologic evidence. The existing information on human health effects comes from studies of acute, intermediate, and chronic exposure primarily by inhalation. The nervous system appears to be particularly susceptible to the effects of toluene. Effects range from reversible acute effects (fatigue, headaches, decrease in manual dexterity, and narcosis) to persistent neurologic impairment in people who abused solvents or inhaled toluene at high concentrations. Subtle alterations in neurologic functions (cognitive functions, hearing, and color discrimination) have been found in workers chronically exposed at lower concentrations.

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Animal and human evidence—alterations in concentrations of hormones (follicle-stimulating hormone, leutenizing hormone, and testosterone) and decreased sperm counts—suggests that toluene may have endocrine-disrupting effects in males and females. However, there are few epidemiologic studies of adverse reproductive effects in humans. Finnish studies of occupational toluene exposure of women or of wives of occupationally exposed men suggested an increased risk of miscarriage, but the studies had a number of limitations. There have been a series of case reports of birth defects in the offspring of women who intentionally inhaled large amounts of toluene or organic solvents during pregnancy. One small Finnish study reported that the opffspring of women occupationally exposed to a mixture of solvents had increases in CNS anomalies.

The ATSDR review included 11 epidemiologic studies of toluene and cancer risk. In general, toluene was not associated with an increased risk of cancer at most sites. Three cohort studies included workers exposed to toluene. They suggested an association with several cancers—including lung cancer, gastric cancer, and colon cancer—but consistent patterns of association with measures of cumulative exposure were not found. Those and other studies also could not rule out confounding by other chemicals, such as benzene.

With regard to other health effects, case reports of solvent abusers have shown some association with cardiac arrhythmia. Other health effects—hematologic, hepatic, or renal—have not been consistently reported.

The toxicology, pharmacokinetics, epidemiology, and health risks associated with exposure have been well documented (EPA 1983a,b, 1990; IARC 1988, 1989; ATSDR 2000b; ACGIH 2007). Chronic exposure to toluene at 50-200 ppm in air can produce neurobehavioral impairments, including impairments in cognitive and neuromuscular performance, hearing, and color discrimination. At higher concentrations, exposure can produce CNS effects, including encephalopathy, headache, fatigue, impairment in coordination, transient memory loss, and impairment in reaction time. Evidence of those effects is found in reports of controlled animal experiments (Dyer et al. 1988; NTP 1990b; von Euler et al. 1993, 2000; Mehta et al. 1998; ATSDR 2000b) and in the epidemiologic literature, especially reports of occupational studies of toluene (Iregren 1982; Orbaek and Nise 1989; Vrca et al. 1997a,b; Cavalleri et al. 2000; Campagna et al. 2001; ACGIH 2007). Results of dosimetric studies of acute behavioral effects of toluene in rats have been used for quantitative comparison of the effects in humans (Benignus et al. 2007; Boyes et al. 2007; Bushnell et al. 2007). There is agreement in the scientific community that toluene is not carcinogenic at lifetime exposures up to 1,200 ppm (NTP 1990b; ATSDR 2000b; Huff 2003). Toluene has had negative results for mutagenicity in a number of test systems (Nestmann et al. 1980; McCarroll et al. 1981). Results of animal studies indicate that toluene is not a teratogenic agent but can retard fetal growth, skeletal development, and behavior of offspring at 1,500 ppm, at which maternal weight gain is also affected (Saillenfait et al. 2007). Another recent study of developmental and reproductive toxicity in rats indicated a NOAEL for maternal toxicity of 750 ppm and a LOAEL of 1,500 ppm for maternal and developmental toxicity (Roberts et al. 2007).

In summary, chronic inhalation exposure to toluene at 50-200 ppm can produce neurobehavioral impairment. Both maternal toxicity and developmental toxicity are observed at the relatively high exposure concentration of 1,500 ppm. Information from well-conducted studies indicates that toluene is not carcinogenic or mutagenic.

VINYL CHLORIDE

The health effects of VC have recently been reviewed by ATSDR (2006). VC is produced primarily (98% of total production) for use in the manufacture of polyvinyl chloride (PVC). PVC materials are used in a variety of products, including automotive parts, packaging products, pipes, and construction material. The primary route of exposure to VC is through ambient air around VC production facilities. It can also be present in groundwater or drinking water because of microbial degradation of other chlorinated

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solvents. However, its rapid volatilization decreases the probability of such exposure of the general population.

The liver appears to be particularly susceptible to the effects of exposure to VC by inhalation. Hepatic damage—such as hepatomegaly, hyperplasia and hypertrophy of hepatocytes and sinusoidal cells, and cirrhosis (independent of alchohol consumption—has been observed. The association between VC and angiosarcoma of the liver (a very rare cancer in humans) has been demonstrated in numerous occupational and animal studies. Other cancer outcomes associated with VC exposure in some studies include hepatocellular carcinoma, cholangiocellular carcinoma, and cancers of the lung and respiratory tract, the lymphatic-hematopoietic system, and the CNS. However, those associations have not been consistent among studies. VC has been classified as "carcinogenic to humans" by IARC (1979, 1987), a "known human carcinogen by the inhalation route of exposure" by EPA (2000), and "known to be a human carcinogen" by the NTP (2005) on the basis of the findings of epidemiologic and animal studies. The key animal data and findings from those reviews are discussed briefly below and are updated with studies published since the reviews were performed.

Additional outcomes have been assessed in epidemiologic studies of workers exposed to VC. Reversible CNS effects—such as dizziness, drowsiness, and headache—have been reported after acute inhalation of high concentrations of VC. Peripheral neuropathy has been reported in workers. Adverse respiratory effects have been observed in some studies but not others. Many of the studies may be confounded by smoking and exposure to PVC resin dust. Development of Raynaud phenomenon (a condition in which the fingers blanch and become numb with discomfort on exposure to cold) has been associated with current occupational exposure. A condition labeled vinyl chloride disease—consisting of Raynaud phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes—has been identified in some VC workers. In some cases, there has been a correlation with immunologic abnormalities. Occupational exposure to VC has also been implicated in alterations in the immune system, including increased percentages of lymphocytes and increased circulating immune complexes (for example, cryoglobulinemia). There is evidence of increased risk of hypertension associated with VC exposurebut no conclusive evidence of an association with coronary heart disease.

Reproductive and developmental effects have also been observed. Case studies have reported sexual impotence and loss of libido in male workers. An increase in pre-eclampsia has been observed. Studies have reported an excess of fetal loss in wives of men exposed to VC. Increases in birth defects—including clubfoot and malformations of the CNS, upper alimentary tract, and genital organs—have been reported in populations exposed to emissions from PVC polymerization facilities.

VC is considered a known human carcinogen mainly on the basis of the consistent observation of excess rates of angiosarcoma of the liver in workers exposed via inhalation.

According to the review by ATSDR, there is limited/suggestive evidence of associations between VC and Raynaud phenomenon, scleroderma-like skin changes, and other immunologic effects. There is inadequate/insufficient evidence to support a conclusion about associations between chronic exposure to VC and reproductive and developmental effects. Specific health effects of VC in animals is discussed below.

Hepatic Toxicity

Hepatic lesions were found in rats exposed chronically to VC in their feed (1.3 mg/kg per day) (Feron et al. 1981; Til et al. 1991). The nonneoplastic lesions included hepatic-cell polymorphism and hepatic cysts. When exposed by inhalation, rats have developed hepatocellular degeneration, hepatic swelling with compression of sinusoids, altered enzyme activity, proliferation of reticulocytes, and increased ratio of liver weight to bodyweight (EPA 2000; ATSDR 2006). Hepatic toxicity is thought to be due to the reactive metabolites of VC that bind to hepatic proteins, DNA, and RNA (ATSDR 2006).

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Renal Toxicity

At high concentrations (300,000 ppm), VC caused renal congestion and degenerative changes. At lower concentrations (3,000 ppm) for longer durations, VC has been reported to increase ratios of renal weight to bodyweight, but this was an inconsistent finding (ATSDR 2006).

Pulmonary Toxicity

At high concentrations, VC is irritating to the respiratory tracts of experimental animals (ATSDR 2006). Chronic-exposure studies have reported a slightly higher incidence of hyperplasia of the olfactory epithelium, increased cellularity of the interalveolar septa, and pulmonary hemorrhage in rats exposed at 5,000 ppm (Feron and Kroes 1979).

Reproductive Toxicity

Some inhalation studies of VC have found effects on male reproduction in rats, including damage to the seminiferous tubules and spermatogenic epithelium, depletion of spermatocytes, disorders of spermatogenesis, and decreases in the ratio of pregnant to mated females at concentrations as low as 100 ppm (Sokal et al. 1980; Bi et al. 1985). Other studies, including a two-generation toxicity study of rats exposed to VC at up to 1,100 ppm (Thornton et al. 2002), did not find such effects. Questions have been raised about the methodology of some studies that reported positive effects (ATSDR 2006). EPA (2000) identified the no-observed-adverse-effect level (NOAEL) for reproductive effects as over 1,100 ppm.

Developmental Toxicity

John et al. (1977, 1981) evaluated the effects of VC on the embryonal and fetal development of mice, rats, and rabbits. Developmental effects were found in mice after in utero exposure to VC. At an inhalation concentration of 500 ppm, the effects included increased fetotoxicity and fetal resorptions, decreased fetal bodyweight, smaller litters, and retarded cranial and sternal ossification. In rats exposed at higher concentrations, an increased incidence of dilated ureters was found in offspring. In both mice and rats, the effects on offspring were observed at concentrations that produced maternal toxicity, as evidenced by increased mortality, reduced bodyweight, and reduced absolute hepatic weight in the dams. No effects were found in rabbits.

No embryo-fetal developmental toxicity was found in a two-generation reproductive-toxicity study of rats exposed to VC at inhalation concentrations up to 1,100 ppm (Thornton et al. 2002).

Neurotoxicity

Like other solvents, VC at high concentrations had neurotoxic effects, such as ataxia, unconsciousness, incoordination, and tremors. After chronic exposure by inhalation (30,000 ppm), rats had decreased responses to external stimuli, surrounding and infiltration of peripheral nerve ends with fibrous tissue, and brain lesions (CalEPA 2000a; ATSDR 2006).

Immunotoxicity

A few studies have reported that VC has an immune-stimulating effect on mice and causes splenomegaly in them (ATSDR 2006). Stimulation of spontaneous lymphocyte transformation was ob-

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served after 2 weeks of exposure at 1,000 ppm and then after 4-8 weeks of exposure at concentrations as low as 10 ppm (Sharma and Gehring 1979).

Genotoxicity

VC is a well-established genotoxicant, having been investigated in a variety of test systems, including in vitro studies of bacteria, fungi, and mammalian cells and in vitro studies of rodents and humans (ATSDR 2006). It has been shown to be mutagenic, and its mutagenicity is enhanced with metabolic activation; this suggests that one of its metabolites is more mutagenic than VC (CalEPA 2000a; ATSDR 2006).

Cancer

VC has been shown to cause cancer in multiple organs and multiple species when inhaled or ingested (IARC 1979; EPA 2000; ATSDR 2006). The association between VC and hepatic angiosarcomas in the epidemiologic literature is supported by similar findings in mice (e.g., Drew et al. 1983), rats (e.g., Feron et al. 1981; Maltoni et al. 1981; Drew et al. 1983; Bi et al. 1985), and hamsters (e.g., Drew et al. 1983). Tumors in rats were found after oral exposure at concentrations as low as 1.7 mg/kg per day.

Other cancers found in rats were Zymbal-gland tumors, mammary-gland tumors, neuroblastomas, and lung tumors (Feron et al. 1981; Maltoni et al. 1981; Drew et al. 1983; Til et al. 1991). Mice exposed by inhalation developed lung tumors, mammary-gland tumors, and angiosarcomas and adenocarcinomas in various sites (Drew et al. 1983). Hamsters also developed hemangiosarcomas, mammary-gland carcinomas, gastric adenocarcinomas, and skin carcinomas (Drew et al. 1983). Some studies have shown that younger rats are more susceptible to the carcinogenicity of VC (Drew et al. 1983; Maltoni and Cotti 1988).

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Appendix E

Details of Epidemiologic Studies on Trichloroethylene and Perchloroethylene

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TABLE E-1 Exposure Information on Epidemiologic Studies Involving Exposure to TCE or PCE

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Aschengrau et al. 2003	Population-based case-control Cape Cod, MA PCE from inner vinyl liner in cement pipes distributing tap water Breast cancer	Relative dose of PCE estimated by algorithm with variables for residential history, water flow (geometry, load on water-distribution system), pipe characteristics (such as pipe diameter, age); inputs determined from maps from local water suppliers or state DEPs	Ever vs never exposed (served by private well for entire Cape Cod residence) Cumulative exposure for each latency period: sum of RDDs for each residence (mass of TCE entering home in tap water over time at each address); categorized as never, low (up to and including median RDD), high RDD (above 50th, 75th, or 99th percentile)	Nine latency periods examined (0, 5, 7, 9, 11, 13, 15, 17, 19 years)
Blair et al. 2003	Cohort study of dry cleaners PCE used as solvent in dry cleaning Cancers, other causes of death	Exposure score for jobs based on published monitoring studies of dry-cleaning industry; scores increased with proximity	Exposure score assigned on basis of jobs held (cleaners, high, score of 40; pressers, sewers, counter workers, score of 7; pickup workers, low, score of 0) Little or no exposure (score of 0) vs medium-high exposure (score of 7 or 40)	Adjustment for age, sex, calendar time
Boice et al. 2006	Cohort of rocket-engine testing-facility workers Hydrazine, TCE All causes of death	All Rocketdyne workers employed on or after Jan. 1, 1948, for 6+ mo at SSFL, nearby facilities (for comparison group); identified from personnel files, work history cards; exposed were test-stand mechanics, inspectors, test-stand engineers, research engineers; personnel listings used to place test-stand mechanics at specific stands in calendar years; descriptive industrial-hygiene information to classify potential exposure to hydrazine, TCE, other chemicals; discussions with workers	Duration of employment (years) (SMR) Potential for exposure (flush engine parts or utility solvent use) (SMR) Duration of employment (RR) 4 decades of employment (RR) Years worked as test-stand mechanic (RR) Years worked with any potential TCE exposure (less than 4 years vs at least 4 years) (RR) Years worked with potential TCE exposure via engine cleaning, weighted by number of engine tests (less than 4 test-years vs at least 4 test-years)	Adjustment for year of birth, year of hire

(Continued)

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TABLE E-1 Continued

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Brüning et al. 2003	Hospital-based case-control	Telephone interview, occupational questionnaire devoted to screw-cutting industry and general for other jobs; TCE, PCE exposure for at least one job period (1+ year), cumulative of TCE in ppm per job per year in job, peaks; assessment semiquantitative for exposure to TCE, PCE; qualitative for other occupational exposures; confidence score (certain, probable, possible) used for each exposure assessed; assessed industry and job-title codes	Ever employed in specific occupations Longest job held Ever worked in tasks, occupations, or industries with TCE or PCE exposure Cumulative exposure assessed with JEM (Pannet et al. 1985): none, low, high (dichotomized at median) Self-reported exposure to TCE, PCE (separately) Occurrence of narcotic symptoms (any, nondaily, or daily) (TCE) Duration of exposure to TCE (none, less than 10 years, 10 to less than 20 years, 20+ years), PCE (none, less than 10 years, 10+ years)	
	West Germany (site of metal, paper, wood-processing industries)			
	TCE, PCE			
	Renal-cell cancer			
Chang et al. 2003	Cohort-mortality study of electronics factory workers	Employment histories at different factories, changes in insurance status from Bureau of Labor Insurance computer database for 1978-1997; confirmed, supplemented with list of names of patients in labor-insurance hospitalization dataset, United Labor Association; duration of employment calculated from insurance records, operation history of index electronics factory (1968-1992); EPA in Taiwan verified pollution of wells with TCE, PCE	Duration of employment (SMR) categorized as 1 year or less, more than 1 year but less than or equal to 5 yrs, more than 5 years) Year of death from cancer (1985-1990, 1991-1997)	
	Taiwan			
	TCE, PCE			
	Cancers			
Charbotel et al. 2006	Case-control	Information from occupational questionnaires, task-exposure matrix for screw-cutting tasks; employee's activity, job title encoded; assessed for exposure to solvents, oils, welding fumes, etc.; semiquantitative assessment for exposure to TCE, qualitative (low, medium, high) for other exposures	By industry (NACE codes) (OR) By Job title (ILO 68 codes) (OR) Ever vs never exposed (OR) Cumulative exposure (ppm-years); task-exposure matrix used to estimate cumulative	Adjustment for tobacco-smoking, BMI
	Arve Valley (France)			
	TCE used as degreasing agent in screw-cutting industry in Arve Valley			

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	Other exposures (chlorinated solvents, oxygenated solvents, white-spirit and petroleum solvents), oils, welding fumes, lead, cadmium, asbestos			dose for each job period (OR) (categorized into tertiles)
	Renal-cell cancer			Cumulative exposure with assessment for peaks (low-medium without peaks, low-medium with peaks, high without peaks, high with peaks) (OR)
				Cumulative exposure with assessment for peaks (low-medium without peaks, low-medium with peaks, high without peaks, high with peaks) with only exposures scored certain or probable summed in cumulative-exposure score (OR)
Costas et al. 2002	Case-control	Exposure assessed based on potential for residence to receive water from contaminated wells G and H, not on actual contaminant concentration in wells; water-distribution model used, validated; cumulative exposure based on exposure periods, operation of wells		With water-distribution model, exposure index developed for each hydraulic area and month (exposure index: fraction of month when contaminated water reached hydraulic area multiplied by fraction of water supplied by contaminated wells)
	Woburn, MA			
	TCE-contaminated groundwater wells in Woburn, MA (site of tannery, chemical manufacturing wastes)			Average, cumulative exposure scores (for seven etiologic windows) categorized as never vs some or never, least, most (median of some exposure used to define least, most)
	TCE (primary), PCE			
	Childhood leukemia			Etiologic windows: entire etiologic period (2 years before conception to date of case diagnosis); preconception period, duration of pregnancy; 1st, 2nd, 3nd trimester of pregnancy; period from time of birth to case diagnosis
De Roos et al. 2001	Case-control (cases identified from hospitals participating in two pediatric collaborative clinical trials)	Self-reported occupational exposures to solvents obtained by telephone interview; industrial-hygienist review of self-reported exposures		Self-reported parental exposure to five categories of chemicals (halogenated hydrocarbons; nonvolatile hydrocarbons; volatile hydrocarbons; paints, inks, pigments; metals, alloys, solders (any vs none)	Adjustment for child's age, maternal race, maternal age, maternal education
	Occupational exposure to five categories of chemicals			
	Neuroblastoma			Industrial hygienist reviewed assessment of exposure on basis of questionnaire data (probable exposure assigned yes, otherwise no)

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TABLE E-1 Continued

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Diot et al. 2002	Hospital-based case-control	Employment periods of over 6 mo recorded from interview, but only employment corresponding to period before patient's diagnosis was included; exposure to various occupational hazards asked; expert committee (occupational physicians, epidemiologists, industrial hygienists) assessed exposure	Ever vs never exposed	
	Central region of France		High cumulative exposure score vs those without high cumulative exposure score	
	Occupational exposures to silica, organic solvents (including TCE)		Cumulative exposure score: sum of exposure scores for each employment	
	Systemic sclerosis		Exposure score: probability x intensity x frequency x duration; probability of exposure: 0 = nonexposure, 0.25 = possible exposure, 0.75 = probable exposure, 1 = certain exposure; intensity of exposure: 0 for nonexposure to 1 for highest level of exposure; length of time worked daily: <10% = 0.05, 10-50% = 0.30, >50% = 0.75; number of years worked	
Fabbro-Peray et al. 2001	Population-based case-control	Cohort interviewed about occupational exposures, including chemicals, pesticides, electromagnetic radiation; asked about smoking; subjects considered exposed if exposure lasted more than 1 year	Self-reported exposure (yes vs no)	Lag time of 5 years before diagnosis (or interview for controls)
	Languedoc-Roussillon, France		Age at first exposure	
	Occupational exposure to benzene, rubber, coal tar, paints, waste oil, dry-cleaning solvents, petroleum products, pesticides		Duration of exposure (never, up to 15 years, over 15 years)	Adjustment for age, sex, urban setting, education
	Non-Hodgkin lymphoma		Cumulative exposure (lifetime-days of exposure) (never-erratic, up to 810 days, over 810 days)	
			Time since first exposure (never, up to 10 years, over 10 years)	
			Further classifications for benzene, pesticides	
Garabrant et al. 2003	Case-control	Women asked whether ever worked at least once a week for 3 mo or more in any of 16 jobs or hobbies that commonly involve solvents; information obtained on job title, years, specific tasks, nine specific solvents (paint thinners and removers, mineral spirits naphtha or white spirits, gasoline, toluene, xylene, benzene, TCE, PCE, trichloroethane), other solvents), safety precautions; reviewed by expert	Self-reported exposure to specific, all solvents	Adjustment for age, year of birth
	Michigan, Ohio		Expert-reviewed exposure to specific, all solvents	
	Occupational or hobby-related exposure to hydrocarbons, chlorinated solvents		Self-reported jobs, hobbies	
	Systemic sclerosis			

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Hansen et al. 2001	Cohort	Historical files of individual air, urinary measurements of TCE exposure (from Labor Inspection Services of Denmark); job information reconstructed from national pension fund	Period of first employment (1947-1964, 1965-1989)		Sensitivity analyses: 10-year, 20-year lag periods (data not shown; no change in results)
	Denmark		Duration of employment (less than 75 mo vs at least 75 mo)		
	TCE		Average personal TCE exposure (less than 19 mg/m^3 vs at least 19 mg/m^3)		
	Cancer		Cumulative TCE exposure (less than 1,080 months-mg/m^3 vs at least 1,080 months-mg/m^3)		
Infante-Rivard et al. 2005	Population-based case-control	Maternal occupational exposures to solvents before and during pregnancy estimated by coding by job for specific contaminants (also called expert method); coded for 21 solvents; home exposure to solvents evaluated on basis of activities, including hobbies, furniture stripping, electronic and motor-vehicle repair, home painting	Jobs held during 2 years before, during pregnancy coded as "possible," "probable," "definite"; level assigned (low = 1, medium = 2, high = 3)		Adjustment for age, education
	Quebec, Canada		Any vs no exposure		
	Maternal occupational exposure to solvents, solvent mixtures		Any vs no exposure (none and "possible" vs "probable" and "definite")		
	Childhood ALL		Level of exposure (0 = baseline, 1 = some exposure (concentration x frequency less than 4), 2 = greater exposure (concentration x frequency at least 4)		
Krishnadasan et al. 2007	Nested case-control	Workers employed 1950-1992 at nuclear-energy, rocket-engine-testing facility; company records used to construct JEM for exposures to hydrazine, TCE, PAHs, benzene, mineral oil; from job-description manuals, walk-throughs, interviews; industrial hygienist created estimate of likelihood, intensity of exposures during three periods (1950s-1960s, 1970s, 1980s-1990s); duration of employment of longest-held job (and others)	Industry-based JEM (for all jobs held)		20-year (and zero lag) exposure estimates
	Nuclear-energy, rocket-engine development, testing facility in Southern California		For each job and by chemical, likelihood (none, low, high), intensity (low, medium, high) for three periods (1950-1969, 1970-1979, 1989-1999)		Adjustment for occupational physical activity, SES, other chemical exposures
	PAHs, TCE, hydrazine, mineral oil, benzene		Cumulative-exposure score for each worker for all jobs held (none, low, moderate, high); cumulative-exposure score = sum of duration of employment x estimated intensity for each job		
	Prostatic cancer		Cumulative-exposure scores categorized by quartiles: unexposed vs low-moderate vs high		

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TABLE E-1 Continued

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Lee et al. 2003	Case-control; residents of two villages in vicinity of electronics factory	Groundwater sampling from off-site residential wells in nearby communities October 1999-May 2000; exposed were downstream residents; stratified on calendar periods based on establishment of factory (allowing 10 years to detect health effects of exposure)	Upstream (referent) vs downstream village (validated by groundwater well samples—detectable vinyl chloride, TCE, PCE, 1,1-dichloroethylene, 1,1,1,-trichloroethane, *cis*-1,2-dichloroethylene, 1,1-dichloroethane)	
	Chlorinated hydrocarbons in groundwater contaminated by hazardous-waste site (formerly electronics factory)		Period of death: 1966-1979 (referent), 1980-1989, 1990-1997	
	Hepatic-cancer mortality			
Lynge et al. 2006	Nested case-control; cohort of laundry, dry-cleaning workers	Occupation code "laundry and dry-cleaning worker" or industry code "laundry and dry cleaning"; categorized on basis of fewer than 10 workers in shop, laundry workers and other workers in dry-cleaning shops; length of employment in shop where worked in 1970 (only the period of 1964-1979 was included); interviews with next of kin; detailed history of dry cleaning in Nordic countries	Exposure categories: unexposed, dry cleaner and other exposed, other in dry cleaning, unclassifiable	
	Denmark, Finland, Norway, Sweden		Dry cleaner length of employment (0-1 years, 2-4 years, 5-9 years, at least 10 years, unknown)	
	Occupational exposure to dry-cleaning solvents (predominantly PCE)			
	Cancer			
Miligi et al. 2006	Population-based case-control study	Job-exposure matrix of most frequent job titles and sectors to assign probability- and intensity-weighted scales of exposure to solvents, five specific categories of chemical classes, eight individual chemicals; occupational history questionnaires	Unexposed vs very low, low and medium, high intensity levels and duration of exposure (15 yr or less vs 15 yr)	Adjustment for sex, age, education, area
	Italy			
	Occupational solvent use in manufacturing industries or agriculture			
	Lymphoma			
Morgan and Cassady 2002	Cohort study of residents with contaminated drinking water	Residence in census tracts near Redlands, CA (where concerns about contamination of groundwater, drinking water with TCE, ammonium perchlorate; 1980 assessment of TCE in Redlands wells ranged from 0.09 to 97 ppb; since 1991, wells either treated or removed to maintain TCE under 5 ppb	None (SIRs—indirect standardization)	
	San Bernardino County, CA (13 census tracts)			
	PCE, chlorate, TCE			
	Cancers			

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Perrin et al. 2007	Cohort study; offspring of dry cleaners	Occupations of parents obtained from birth certificate	Mother and/or father dry cleaner(s) at time of birth (yes vs no)	
	Jerusalem, Israel			
	Maternal or paternal occupational (dry-cleaning) exposure to TCE			
	Schizophrenia in offspring			
Raaschou-Nielsen et al. 2003	Cohort	Employment based on companies classified by air TCE measurements in workplace 1947-1989 by Danish Labor Inspection Service, area and personal measurements (after 1974);included companies determined by size; iron and metal, electronics, painting, printing, chemical, dry cleaning, other; workers identified by Pension Fund or Central Population Registry (most recent job title)	Duration of employment (less than 1 year, 1-4.9 years, *at least* 5 years)	Stratified analysis by sex
	Denmark		Year of first employment (before 1970, 1970-1979, 1980-)	
	TCE		Lag time (none, 20 years)	
	Cancers, including non-Hodgkin lymphoma, renal-cell carcinoma, esophageal adenocarcinoma		Number of employees (fewer than 50, 50-99, 100-200)	
Radican et al. 2006	Retrospective cohort; aircraft workers	Subjects identified from database of former civilian employees of Hill Air Force Base I, Utah; semiquantitative estimate of TCE exposure obtained from comprehensive exposure assessment; cumulative exposure score computed for each subject	Cumulative-exposure score: frequency (times/day), duration (min/day), calendar period of use, years of exposure; categorized into tertiles	
	TCE, 1,1,1-trichloroethane, methylene chloride, carbon tetrachloride, JP4 gasoline, Freon, isopropyl alcohol, acetone, toluene, methyl ethyl ketone, *o*-dichlorobenzene, PCE, chloroform, stoddard solvent, styrene, xylene			
	End-stage renal disease			

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TABLE E-1 Continued

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Ruder et al. 2001 (in IOM report)	Cohort study; dry-cleaning workers	Dry-cleaning union records , people not known to ever have been exposed to carbon tetrachloride who had worked 1+ year before 1960 in shop using PCE; shops visited to verify solvent use history; PCE-only subcohort, PCE-plus cohort (records inadequate to confirm PCE use or another solvent, mostly Stoddard solvent or other petroleum solvents)	Time since first employment (less than 20 years, at least 20 years), duration of employment in dry-cleaning shops (1-5 years, 5+ years)	
	San Francisco, Oakland, CA; Chicago, IL; Detroit, MI; New York, NY		PCE only solvent, PCE and other solvents used in dry-cleaning shops	
	Occupational exposure to PCE			
	Cancer deaths			
Schreiber et al. 2002	Cross-sectional; residents above dry-cleaning shops, day-care workers sharing building with dry cleaner compared with NY State Department of Health controls, matched by age (within 2 years), sex	Apartment residents above dry cleaner; air sampling of PCE in apartments; day-care workers sharing building with dry cleaner	Personal monitoring of PCE with passive monitors (3M organic vapor monitors) for exposed persons	
			Creatinine-adjusted urinary PCE, trichloroacetic acid, trichloroethanol for exposed persons	
	PCE		Exposed vs control groups	
	Visual contrast sensitivity			
Seidler et al. 2007	Population-based case-control	Complete occupational history obtained by interview: dates, job title, industry, job tasks, job-task-specific supplementary questions; industrial physician assessed intensity, frequency of exposure to specific chlorinated hydrocarbons (including TCE, PCE), aromatic hydrocarbons	Intensity of exposure (low, medium, high—assigned in ppm depending on chemical); frequency of exposure based on 40-h workweek (low = 1-5%, medium = over 5 to 30%, high = over 30%); confidence (possible but not probable, probable, certain)	
	Germany			
	Occupational exposure to chlorinated, organic solvents			
	Lymphoma		Cumulative exposure (ppm x years): sum of intensity x frequency x duration for all jobs held; categorized among controls at 50th, 90th percentiles	
Sonnefeld et al. 2001	Case-control	Residents of Tarawa Terrace were considered exposed; exposure magnitude determined by length of residence	Duration of exposure (never exposed, 1-3 weeks, 4-10 weeks, 11-20 weeks, over 20 weeks and less than entire pregnancy, entire pregnancy and less than 1 year before LMP, entire pregnancy and at least 1 year before LMP	
	Camp Lejeune, NC			
	Contaminated drinking-water TCE, other compounds			
	Birthweight, small for gestational age, preterm birth			

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Sung et al. 2007	Retrospective cohort; female workers at electronics factory Taoyuan, Taiwan Occupational exposure to solvents Cancer	Female workers of former electronics factory identified through Bureau of labor Insurance 1973-1997; duration of employment	Duration of employment (less than 1 mo, 1-11 mo, 1-4 years, 5-9 years, at least 10 years)	Latency accounted for in assessing person-years at risk (5 years, cancer of thyroid, leukemia; 15 years, breast cancer; 10 years, other cancers) Stratified by calendar year (in which regulations were enacted on use of organic solvents in factories): before and after June 20, 1974
Vieira et al. 2005	Population-based case-control Cape Cod, MA PCE from inner vinyl liner leaching from cement pipes distributing tap water Breast cancer	Used personal delivered-dose model that included personal data on tap-water consumption, bathing habits from subjects or next of kin	PDD: sum of PCE from inhalation, dermal absorption, ingestion based on RDD; categorized into four groups based on distribution among exposed controls: at least 50th percentile, over 50th percentile, over 75th percentile, over 90th percentile; ever vs never exposed Inhalation exposure: function of temperature, frequency, duration of baths, showers, concentration of PCE volatilized in air from water Dermal absorption: function of surface area, Fick's law Ingestion: function of volume of tap water consumed	Nine latency periods examined (0, 5, 7, 9, 11, 13, 15, 17, 19 years) Adjustment for age at diagnosis or index year, family history of breast cancer, personal history of breast cancer, age at first live birth or stillbirth, occupational exposure to PCE
Yauck et al. 2004	Case-control Milwaukee, WI TCE-emitting sites in Milwaukee, surrounding areas, 1996-1999 Congenital heart defects	GIS used to calculate distances between maternal residence, TCE sites; classification tree analysis used to determine distance for dichotomizing exposure: within or outside 1.32 miles of at least one TCE site	Proximity measure using classification-tree method: distance from maternal residence to TCE-emitting facility dichotomized into exposed (residence within 1.32 miles of at least one site), nonexposed (residence more than 1.32 miles of at least one site	

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TABLE E-1 Continued

Reference	Study Design, Exposure, Outcomes	Exposure Assessment	Exposure Metrics	Comments
Zhao et al. 2005	Retrospective cohort; Rockwell/Rocketdyne (now Boeing) aerospace male workers employed before 1980 Los Angeles, CA Hydrazine, TCE, PAHs, mineral oil, benzene Cancer mortality, incidence	California aerospace workers 1950-1993 at several Boeing North America facilities in LA, employed before 1980 in aerospace division of SSFL, worked 2+ years and never monitored for radiation exposure; extensive industrial-hygienist review interested in exposure to rocket fuel hydrazine, TCE, PAHs, mineral oil, benzene	JEM used to assess exposure in each job group: Intensity (0-3) (1950-1969, 1970-1979, 1980-1989) × duration Cumulative-exposure score: low (up to 3), medium (over 3 up to 12), high (over 12)	Adjustment for time since first employment, SES, age at diagnosis

Abbreviations: ALL = acute lymphocytic leukemia, BMI = body-mass index, DEP = Department of Environmental Protection, EPA = U.S. Environmental Protection Agency, GIS = geographic information system, ILO = International Labor Organization, IOM = Institute of Medicine, JEB = job-exposure matrix, LMP = last menstrual period, OR = odds ratio, PAH = polycyclic aromatic hydrocarbon, PCE = perchloroethylene, PDD = personal delivered dose, RDD = relative delivered dose, RR = relative risk, SES = socioeconomic status, SIR = standardized incidence ratio, SMR = standardized mortality ratio, SSFL = Santa Susana Field Laboratory, TCE = trichloroethylene

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TABLE E-2 Studies of Cancer End Points and Exposure to TCE

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
BUCCAL CAVITY AND PHARYNGEAL CANCER			
Cohort Studies—Incidence			
Hansen et al. 2001[a]	Danish workers:		
	Men	7	2.3 (0.9-4.7) SIR
	Women	0	—
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	95	1.1 (0.90-1.36) SIR
	Women employed at least 3 mo	10	1.8 (0.84-3.24) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	19	0.55 (0.33-0.86) SIR
	Women	42	0.96 (0.69-1.29) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	10[b]	0.74 (0.35-1.36) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	6	0.65 (0.50-0.83) SMR
	Women	10	0.71 (0.34-1.30) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	4	1.25 (0.34-3.21) SMR
ESOPHAGEAL CANCER			
Cohort Studies—Incidence			
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men:		
	All employed at least 3 mo	23	1.8 (1.5-2.73) SIR
	Employed <1 year	6	1.7 (0.6-3.6) SIR
	Employed 1-4.9 years	9	1.9 (0.9-3.6) SIR
	Employed ≥5 years	8	1.9 (0.8-3.7) SIR
	Women:		
	All employed at least 3 mo	0	0 (0.00-8.32) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	9	1.00 SIR
	Medium (>3-15)	8	1.66 (0.62-4.41) SIR
	High (>15)	2	0.82 (0.17-3.95) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	2	1.16 (0.14-4.20) SIR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	18	1.00 SMR
	Medium (>3-15)	15	1.40 (0.70-2.82) SMR
	High (>15)	7	1.27 (0.52-3.13) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	3	0.88 (0.18-2.58) SMR
STOMACH CANCER			
Cohort Studies—Incidence			
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	77	1.0 (0.80-1.27) SIR
	Women employed at least 3 mo	9	1.3 (0.59-2.46) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	56[c]	0.73 (0.55-0.95) SIR
	Women	135[c]	0.93 (0.78-1.09) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	42	0.88 (0.64-1.19) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	7	0.93 (0.37-1.91) SMR
	Women	24	1.11 (0.71-1.65) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	6	1.37 (0.50-2.99) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	39	2.18 (0.97-4.89) MOR
COLON CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	327[d]	0.86 (99%CI 0.74-0.99) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	142	0.9 (0.77-1.08) SIR
	Women employed at least 3 mo	35	1.2 (0.85-1.70) SIR

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Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	49	1.00 SIR
	Medium (>3-15)	28	0.93 (0.58-1.50) SIR
	High (>15)	13	0.92 (0.49-1.72) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	98[d]	1.10 (0.89-1.34) SIR
	Employed before June 1974[e]	21[d]	1.02 (0.63-1.56) SIR
	Employed after June 1974[e]	77[d]	1.12 (0.88-1.40) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	3	0.65 (0.13-1.91) SMR
	Women	19	1.36 (0.82-2.13) SMR
	Employed <1 year (men and women)	12	1.33 SMR
	Employed 1-5 years (men and women)	3	0.85 SMR
	Employed >5 years (men and women)	4	2.94 SMR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	36[d]	1.00 SMR
	Medium (>3-15)	18[d]	0.90 (0.51-1.60) SMR
	High (>15)	8[d]	0.76 (0.35-1.68) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	13[d]	1.08 (0.58-1.85) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	26[d]	0.83 (0.24-2.89) MOR
RECTAL CANCER			
Cohort Studies—Incidence			
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	128	1.1 (0.95-1.35) SIR
	Women employed at least 3 mo	15	1.1 (0.62-1.84) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.73 (0.08-2.65) SMR
	Women	13	1.67 (0.89-2.85) SMR
	Employed <1 year (men and women)	9	1.81 SMR
	Employed 1-5 years (men and women)	2	1.01 SMR
	Employed >5 years (men and women)	2	2.50 SMR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
HEPATIC CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	28[f]	1.29 (99%CI 0.74-2.05) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men:		
	All employed at least 3 mo	27	1.1 (0.74-1.64) SIR
	Employed <1 year	9	1.3 (0.6-2.5) SIR
	Employed 1-4.9 years	9	1.0 (0.5-1.9) SIR
	Employed ≥5 years	9	1.1 (0.5-2.1) SIR
	Women:		
	All employed at least 3 mo	7	2.8 (1.13-5.80) SIR
	Employed <1 year	2	2.8 (0.3-10.0) SIR
	Employed 1-4.9 years	4	4.1 (1.1-10.5) SIR
	Employed ≥5 years	1	1.3 (0.0-7.1) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	36[f]	0.79 (0.55-1.10) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Boice et al. 2006	Male workers at rocket-engine testing facility	4[f]	1.28 (0.35-3.27) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	53	2.57 (1.21-5.46) MOR
PANCREATIC CANCER			
Cohort Studies—Incidence			
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	66	1.1 (0.85-1.39) SIR
	Women employed at least 3 mo	9	1.0 (0.47-1.96) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	13	1.00 SIR
	Medium (>3-15)	7	0.85 (0.33-2.17) SIR
	High (>15)	1	0.28 (0.04-2.14) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	11	1.64 (0.82-2.94) SIR

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Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.49 (0.01-2.73) SMR
	Women	5	1.39 (0.45-3.25) SMR
	Employed <1 year (men and women)	2	0.91 SMR
	Employed 1-5 years (men and women)	2	2.15 SMR
	Employed >5 years (men and women)	1	2.22 SMR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	22	1.00 SMR
	Medium (>3-15)	15	1.13 (0.58-2.21) SMR
	High (>15)	2	0.35 (0.08-1.50) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	2	0.32 (0.04-1.14) SMR
LARYNGEAL CANCER			
Cohort Studies—Incidence			
Hansen et al. 2001[a]	Danish workers:		
	Men	2	1.1 (0.1-3.9) SIR
	Women	0	—
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	53	1.2 (0.87-1.52) SIR
	Women employed at least 3 mo	3	1.7 (0.33-4.82) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Boice et al. 2006	Male workers at rocket-engine testing facility	2	1.45 (0.18-5.25) SMR
LUNG CANCER			
Cohort Studies—Incidence			
Hansen et al. 2001[a]	Danish workers:		
	Men	16	0.8 (0.5-1.3) SIR
	Women	1	0.7 (0.01-3.8) SIR
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	356[g]	0.71 (99%CI 0.61-0.81) SIR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	20	0.94 (0.57-1.45) SIR
	Women	34	0.95 (0.66-1.33) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men:		
	All employed at least 3 mo	559	1.4 (1.28-1.51) SIR
	Employed <1 year	181	1.6 (1.4-1.9) SIR
	Employed 1-4.9 years	193	1.3 (1.1-1.5) SIR
	Employed ≥5 years	185	1.4 (1.2-1.6) SIR
	Women:		
	All employed at least 3 mo	73	1.9 (1.48-2.35) SIR
	Employed <1 year	28	2.5 (1.6-3.6) SIR
	Employed 1-4.9 years	25	1.6 (1.1-2.4) SIR
	Employed ≥5 years	20	1.6 (1.0-2.5) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	43	1.00 SIR
	Medium (>3-15)	35	1.36 (0.86-2.14) SIR
	High (>15)	14	1.11 (0.60-2.06) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	46[h]	0.92 (0.67-1.23)
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	13[h]	0.90 (0.48-1.53) SMR
	Women	25[h]	1.01 (0.65-1.49) SMR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	99	1.00 SMR
	Medium (>3-15)	62	1.05 (0.76-1.44) SMR
	High (>15)	33	1.02 (0.68-1.53) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	51[h]	1.24 (0.92-1.63) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	41	1.75 (0.79-2.39) MOR
BONE CANCER			
Cohort Studies—Incidence			

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Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.61 (0.01-3.39) SIR
	Women	6	1.28 (0.47-2.78) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	3	0.92 (0.19-2.70) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0[i]	—
	Women	4[i]	1.63 (0.44-4.18) SMR
	Employed <1 year (men and women)	2[i]	1.25 SMR
	Employed 1-5 years (men and women)	2[i]	3.23 SMR
	Employed >5 years (men and women)	0[i]	—
Boice et al. 2006	Male workers at rocket-engine testing facility	0	0 (0.00-13.8) SMR
SOFT-TISSUE SARCOMA			
Cohort Study—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	3	1.4 (0.3-4.2) SIR
	Women	8	1.0 (0.4-2.0) SIR
Cohort Study—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
BREAST CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water (women only)	536	1.09 (99%CI 0.97-1.21) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	2	0.5 (0.06-1.90) SIR
	Women employed at least 3 mo	145	1.1 (0.89-1.24) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	0.00 (0.00-33.54) SIR
	Women	215	1.19 (1.03-1.36) SIR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	286	1.09 (0.96-1.22) SIR
	Employed before June 1974[e]	90	1.38 (1.11-1.70) SIR
	Employed after June 1974[e]	196	0.99 (0.85-1.14) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	51	1.14 (0.85-1.51) SMR
	Employed <1 year (women)	31	1.08 SMR
	Employed 1-5 years (women)	14	1.25 SMR
	Employed >5 years (women)	6	1.32 SMR
CERVICAL CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	29	0.65 (99%CI 0.38-1.02) SIR
Raaschou-Nielsen et al. 2003	Danish workers (women employed for at least 3 mo)	62	1.9 (1.42-2.37) SIR
	Employed <1 year	30	2.5 (1.7-3.5) SIR
	Employed 1-4.9 years	22	1.6 (1.0-2.4) SIR
	Employed ≥5 years	10	1.3 (0.6-2.4) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):		
	Employed <1 year	177	1.1 (0.9-1.2) SIR
	Employed 1-5 years	69	1.1 (0.8-1.3) SIR
	Employed 5-10 years	26	1.6 (1.1-2.4) SIR
	Employed >10 years	1	0.1 (0.0-0.8) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	337	0.96 (0.86-1.06) SIR
	Employed before June 1974[e]	72	0.84 (0.66-1.06) SIR
	Employed after June 1974[e]	265	0.99 (0.88-1.12) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE and PCE (women)	21	0.80 (0.49-1.22) SMR
	Employed <1 year	14	0.84 SMR
	Employed 1-5 years	6	0.89 SMR
	Employed >5 years	1	0.34 SMR
UTERINE CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	124	1.35 (99%CI 1.06-1.70) SIR

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Raaschou-Nielsen et al. 2003	Danish workers (women employed at least 3 mo)	24	1.0 (0.66-1.53) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE	337[j]	1.06 (0.95-1.18) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	25	0.96 (0.62-1.42) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):	5	0.91 (0.29-2.13) SMR
	Employed <1 year	3	0.88 SMR
	Employed 1-5 years	2	1.42 SMR
	Employed >5 years	0	—
OVARIAN CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	81	1.16 (99%CI 0.85-1.53) SIR
Raaschou-Nielsen et al. 2003	Danish workers (w omen employed at least 3 mo)	22	0.9 (0.55-1.32) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	36[k]	0.83 (0.58-1.15) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):	7	0.80 (0.32-1.64) SMR
	Employed <1 year	1	0.18 SMR
	Employed 1-5 years	3	1.36 SMR
	Employed >5 years	3	3.45 SMR
PROSTATIC CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	483	1.11 (99%CI 0.98-1.25) SIR
Raaschou-Nielsen et al. 2003	Danish workers (men employed at least 3 mo)	163	0.9 (0.79-1.08) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (men)	0	—
Boice et al. 2006	Male workers at rocket-engine testing facility	8	0.82 (0.36-1.62) SMR
Case-Control Studies			
Krishnadasan et al. 2007	Workers at nuclear energy and rocket-engine testing facility:		
	Low-moderate exposure, lag 0	90	1.3 (0.81-2.1) OR
	High exposure, lag 0	45	2.1 (1.2-3.9) OR
TESTICULAR CANCER			
Cohort Studies—Incidence			
Hansen et al. 2001[a]	Danish workers (men)	1	0.7 (0.01-4.0) SIR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
Raaschou-Nielsen et al. 2003	Danish workers (men employed at least 3 months)	93	1.1 (0.92-1.40) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE	1[l]	0.14 (0.00-0.76) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (men)	0	—
Boice et al. 2006	Male workers at rocket-engine testing facility	0[l]	0 (0.00-8.53) SMR
RENAL CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	54	0.80 (99%CI 0.54-1.12) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men		
	All employed at least 3 mo	93	1.2 (0.97-1.48) SIR
	Employed <1 year	14	0.8 (0.5-1.4) SIR
	Employed 1-4.9 years	25	1.2 (0.8-1.7) SIR
	Employed ≥5 years	29	1.6 (1.1-2.3) SIR
	Women:		
	All employed at least 3 mo	10	1.2 (0.55-2.11) SIR
	Employed <1 year	2	1.1 (0.1-3.8) SIR
	Employed 1-4.9 years	3	1.2 (0.2-3.4) SIR
	Employed ≥5 years	3	1.5 (0.3-4.3) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	8[m]	1.06 (0.45-2.08) SIR
	Women	12[m]	1.09 (0.56-1.91) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	6	1 SIR
	Medium (>3-15)	6	1.87 (0.56-6.20) SIR
	High (>15)	4	4.90 (1.23-19.6) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	15[m]	1.10 (0.62-1.82) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0[m]	—
	Women	3[m]	1.18 (0.24-3.44) SMR
	Employed <1 year	1[m]	0.62 SMR

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	Employed 1-5 years	2[m]	3.08 SMR
	Employed >5 years	0[m]	—
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	7	1 SMR
	Medium (>3-15)	7	1.43 (0.49-4.16) SMR
	High (>15)	3	2.03 (0.50-8.32) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	7	2.22 (0.89-4.57) SMR
Case-Control Studies			
Brüning et al. 2003	Hospital-based study in Arnsberg, Germany:		
	Longest-held job (men and women)	117	1.80 (1.01-3.20) OR
	Ever employed in:		
	Metal greasing, degreasing	15	5.57 (2.33-13.32) OR
	Metal processing	30	1.34 (0.81-2.23) OR
	Metalworking	9	2.33 (0.91-5.94) OR
	Pannett job-exposure matrix:		
	Degreasing agents:		
	Low	9	2.11 (0.86-5.18) OR
	High	7	1.01 (0.40-2.54) OR
	Solvents:		
	Low	8	1.80 (0.70-4.59) OR
	High	8	1.45 (0.59-3.58)OR
	Self-reported exposure	25	2.47 (1.36-4.49) OR
	Self-reported narcotic symptoms	19	3.71 (1.80-7.54) OR
	Duration of self-reported exposure:		
	None	109	1 OR
	<10 years	11	3.78 (1.54-9.28) OR
	10-20 years	7	1.80 (0.67-4.79) OR
	>20 years	6	2.69 (0.84-8.66) OR
Charbotel et al. 2006	Cases in Arve Valley, France:		
	Exposed during at least one job period:		
	Nonexposed	49	1 OR
	Exposed	37	1.64 (0.95-2.84) OR
	Cumulative dose:		
	Low	12	1.62 (0.75-3.47) OR
	Medium	9	1.15 (0.47-2.77) OR
	High	16	2.16 (1.02-4.60) OR
	Cumulative dose peaks:		

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
	Low-medium, no peaks	18	1.35 (0.69-2.63) OR
	Low-medium, with peaks	3	1.61 (0.36-7.30) OR
	High, no peaks	8	1.76 (0.65-4.73) OR
	High, with peaks	8	2.73 (1.06-7.07) OR
BLADDER CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	82	0.98 (99%CI 0.71-1.29) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	203	1.0 (0.89-1.18) SIR
	Women employed at least 3 mo	17	1.6 (0.93-2.57) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	20	1.00 SIR
	Medium (>3-15)	19	1.54 (0.81-2.92) SIR
	High (>15)	11	1.98 (0.93-4.22) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	3	0.34 (0.07-1.00) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.96 (0.01-5.36) SIR
	Women	1	0.96 (0.01-5.33) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative exposure score, lag 0:		
	Low (0-3)	8	1.00 SMR
	Medium (>3-15)	6	1.27 (0.43-3.73) SMR
	High (>15)	3	1.15 (0.29-4.51) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	5[n]	1.66 (0.54-3.87) SMR
SKIN MELANOMAS			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	137	1.42 (99%CI 1.13-1.77) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men:		
	All employed at least 3 mo	56	0.7 (0.55-0.94) SIR
	Employed <1 year	17	0.6 (0.4-1.0) SIR
	Employed 1-4.9 years	26	0.9 (0.6-1.3) SIR
	Employed ≥5 years	13	0.6 (0.3-1.0) SIR

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	Women:		
	All employed at least 3 mo	16	0.8 (0.44-1.24) SIR
	Employed <1 year	9	1.2 (0.6-2.3) SIR
	Employed 1-4.9 years	3	0.4 (0.1-1.0) SIR
	E mployed ≥5 years	4	0.8 (0.2-2.1) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.48 (0.05-1.73) SIR
	Women	13	0.99 (0.53-1.69) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	17	1.00 SIR
	Medium (>3-15)	15	1.44 (0.71-2.92) SIR
	High (>15)	4	0.87 (0.29-2.64) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	22	1.03 (0.65-1.56) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Boice et al. 2006	Male workers at rocket-engine testing facility	0	0 (0.00-1.51) SMR
CENTRAL NERVOUS SYSTEM CANCER			
Cohort Studie—Incidence			
Hansen et al. 2001[a]	Danish workers:		
	Men	1	0.4 (0.01-2.1) SIR
	Women	0	—
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	37	1.54 (99%CI 0.96-2.31) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	85	1.0 (0.76-1.18) SIR
	Women employed at least 3 mo	19	1.1 (0.67-1.74) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.40 (0.05-1.46) SIR
	Women	15	0.97 (0.54-1.61) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	7[o]	1.00 SIR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
	Medium (>3-15)	2[o]	0.46 (0.09-2.25) SIR
	High (>15)	1[o]	0.47 (0.06-3.95) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan:		
	Brain	14	1.07 (0.59-1.80) SIR
	Other parts of nervous system	2	1.43 (0.17-5.17) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.48 (0.01-2.66) SMR
	Women	6	0.91 (0.33-1.99) SMR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	12[o]	1.00 SMR
	Medium (>3-15)	3[o]	0.42 (0.12-1.50) SMR
	High (>15)	3[o]	0.83 (0.23-3.08) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	3	0.81 (0.17-2.36) SMR
CENTRAL NERVOUS SYSTEM CANCER IN CHILDREN			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	6	1.05 (99%CI 0.24-2.70) SIR
LYMPHATIC AND HEMATOPOIETIC CANCER			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	6	0.73 (0.27-1.60) SIR
	Women	16	0.65 (0.37-1.05) SIR
MALIGNANT LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-year	40	0.7 (0.4-1.1) OR
	>4.4 to ≤35 ppm-year	32	0.7 (0.5-1.2) OR
	>35 ppm-year	21	2.1 (1.0-4.8) OR
NON-HODGKIN LYMPHOMA			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	111	1.09 (99%CI 0.84-1.38) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		

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	Men:		
	All employed at least 3 mo	83	1.2 (0.98-1.52) SIR
	Employed <1 year	23	1.1 (0.7-1.6) SIR
	Employed 1-4.9 years	33	1.3 (0.9-1.8) SIR
	Employed ≥5 years	27	1.4 (0.9-2.0) SIR
	Women:		
	All employed at least 3 mo	13	1.4 (0.73-2.34) SIR
	Employed <1 year	2	0.7 (0.1-2.4) SIR
	Employed 1-4.9 years	6	1.6 (0.6-3.5) SIR
	Employed ≥5 years	5	1.8 (0.6-4.3) SIR
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	28	1.00 SIR
	Medium (>3-15)	16	0.88 (0.47-1.65) SIR
	High (>15)	1	0.20 (0.03-1.46) SIR
Cohort Studies—Mortality			
Zhao et al. 2005	Aerospace workers (men)		
	Cumulative-exposure score, lag 0:		
	Low (0-3)	27	1.00 SMR
	Medium (>3-15)	27	1.49 (0.86-2.57) SMR
	High (>15)	6	1.30 (0.52-3.23) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	1	0.21 (0.01-1.18) SMR
Case-Control Studies			
Miligi et al. 2006	Cases with occupational exposure in Italy:		
	Very low-low	35	0.8 (0.5-1.3) OR
	Medium-high	35	1.2 (0.7-2.0) OR
	≤15 years	22	1.1 (0.6-2.1) OR
	>15 years	12	1.0 (0.5-2.6) OR
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	B-non-Hodgkin lymphoma:		
	>0 to ≤4.4 ppm-years	32	0.7 (0.5-1.2) OR
	>4.4 to ≤35 ppm-years	27	0.8 (0.5-1.3) OR
	>35 ppm-years	17	2.3 (1.0-5.3) OR
	T-non-Hodgkin lymphoma:		
	>0 to ≤4.4 ppm-years	2	0.7 (0.2-3.3) OR
	>4.4 to ≤35 ppm-years	2	1.1 (0.2-5.1) OR
	>35 ppm-years	2	4.7 (0.8-26.1) OR

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
HODGKIN DISEASE			
Cohort Studies—Incidence			
Hansen et al. 2001[a]	Danish workers:		
	Men	0	—
	Women	0	—
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	17	0.93 (99%CI 0.44-1.67) SIR
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	18	0.9 (0.51-1.37) SIR
	Women employed at least 3 mo	2	0.8 (0.09-3.00) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	1	2.23 (0.03-12.40) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	2	2.86 (0.35-10.3) SMR
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	6	0.4 (0.2-1.1) OR
	>4.4 to ≤35 ppm-years	3	0.4 (0.1-1.4) OR
	>35 ppm-years	2	2.0 (0.4-10.5) OR
MULTIPLE MYELOMA			
Cohort Studies—Incidence			
Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	28	1.1 (0.70-1.52) SIR
	Women employed at least 3 mo	3	0.9 (0.18-2.56) SIR
Cohort Studies—Mortality			
Boice et al. 2006	Male workers at rocket-engine testing facility	1	0.50 (0.01-2.77) SMR
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	3	0.5 (0.2-1.9) OR
	>4.4 to ≤35 ppm-years	6	1.0 (0.4-2.7) OR
	>35 ppm-years	1	0.7 (0.1-5.5) OR
LEUKEMIA			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	77[p]	1.02 (99%CI 0.74-1.35) SIR

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Raaschou-Nielsen et al. 2003	Danish workers:		
	Men employed at least 3 mo	69	1.1 (0.84-1.37) SIR
	Women employed at least 3 mo	13	1.7 (0.89-2.86) SIR
Sung et al. 2007	Female electronics workers in Taoyuan, Taiwan	23	0.78 (0.49-1.17) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.44 (0.05-1.59) SMR
	Women	8	0.54 (0.23-1.07) SMR
Boice et al. 2006	Male workers at rocket-engine testing facility	5[q]	1.08 (0.35-2.53) SMR
CHRONIC LYMPHOCYTIC LEUKEMIA			
Cohort Studies—Mortality			
Boice et al. 2006	Male workers at rocket-engine testing facility	1	1.19 (0.03-6.61) SMR
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	10	1.1 (0.5-2.4) OR
	>4.4 to ≤35 ppm-years	6	0.7 (0.3-1.7) OR
	>35 ppm-years	2	0.9 (0.2-4.5) OR
LEUKEMIA OTHER THAN CHRONIC LYMPHOCYTIC LEUKEMIA			
Cohort Studies—Mortality			
Boice et al. 2006	Male workers at rocket-engine testing facility	4	1.05 (0.29-2.69) SMR
DIFFUSE LARGE B-CELL LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	6	0.5 (0.2-1.2) OR
	>4.4 to ≤35 ppm-years	7	0.8 (0.3-1.8) OR
	>35 ppm-years	4	2.6 (0.7-3.0) OR
FOLLICULAR LYMPHOMA			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	7	1.3 (0.5-3.2) OR
	>4.4 to ≤35 ppm-years	3	0.7 (0.2-2.6) OR
	>35 ppm-years	3	3.2 (0.8-12.9) OR
MARGINAL ZONE LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤4.4 ppm-years	2	0.9 (1.2-4.3) OR

(Continued)

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TABLE E-2 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, SIR, or SMR (95% CI)
	>4.4 to ≤35 ppm-years	2	4.2 (0.8-23.9) OR
	>35 ppm-years	2	4.2 (0.8-23.9)
CHILDHOOD LEUKEMIA			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	10	1.09 (99%CI 0.38-2.31) SIR
Case-Control Studies			
Costas et al. 2002	Cases in Woburn, MA (drinking water contaminated with TCE, PCE, other chemicals):		
	Ever exposed:		
	From 2 years before conception to case diagnosis	16	2.39 (0.54-10.59) OR
	During 2 years before conception	8	2.61 (0.47-14.37) OR
	During pregnancy	10	8.33 (0.73-94.67) OR
	From birth to diagnosis	12	1.18 (0.28-5.05) OR
	Cumulative exposure:		
	From 2 years before conception to case diagnosis		
	Least exposed	9	5.00 (0.75-33.50) OR
	Most exposed	7	3.56 (0.51-24.78) OR
	During 2 years before conception		
	Least exposed	4	2.48 (0.42-15.22) OR
	Most exposed	4	2.82 (0.30-26.42) OR
	During pregnancy		
	Least exposed	3	3.53 (0.22-58.14) OR
	Most exposed	7	14.30 (0.92-224.52) OR
	From birth to diagnosis		
	Least exposed	7	1.82 (0.31-10.84) OR
	Most exposed	5	0.90 (0.18-4.56) OR

[a]Hansen et al. (2001) study not cited in IOM (2003) report analysis for this particular cancer outcome, so included here as new information.
[b]Oral cavity.
[c]Digestive organs and peritoneum.
[d]Colon and rectum.
[e]Month and date when regulations on solvent use were promulgated.
[f]Results are for hepatic and biliary cancer combined.
[g]Lungs and bronchi.
[h]Trachea, bronchi, and lungs.
[i]Bone and articular cartilage.
[j]Female genital organs.
[k]Ovaries, fallopian tubes, and broad ligaments.

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[l]Testes and other male genital organs.
[m]Kidneys and other unspecified urinary organs.
[n]Bladder and other urinary cancers.
[o]Brain cancer only.
[p]All leukemias.
[q]Leukemia and aleukemia.
Abbreviations: CI = confidence interval, MOR = mortality odds ratio, OR = odds ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio.

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TABLE E-3a Studies of Noncancer End Points and Exposure to TCE

Reference	Study Population	No. Exposed Persons	OR (95% CI)
END-STAGE RENAL DISEASE			
Cohort Studies			
Radican et al. 2006	Aircraft workers (1973-2000)	56	1.91 (1.08-3.38)
	Aircraft workers (1973-2002)[a]	61	1.42 (0.87-2.31)
SYSTEMIC SCLEROSIS			
Case-Control Studies			
Diot et al. 2002	Hospital-based study in Tours, France		
	Men and women with occupational exposure:	13	2.39 (1.04-5.22)
	Men	7	4.67 (0.99-21.89)
	Women	6	2.10 (0.65-6.75)
	High final cumulative exposure (men and women)	7	7.58 (1.54-37.36)
Garabrant et al. 2003	Women in Michigan and Ohio:		
	Self-reported exposure	8	2.0 (0.8-4.8)
	Expert-confirmed exposure	4	1.9 (0.6-6.6)
CONGENITAL HEART DEFECTS			
Case-Control Studies			
Yauck et al. 2004	Infants born in Milwaukee, WI (1997-1999):		
	Maternal age, TCE exposure		
	<38 years, nonexposed		1
	<38 years, exposed		0.9 (0.6-1.2)
	≥38 years, nonexposed		1.9 (1.1-3.5)
	≥38 years, exposed		6.2 (2.6-14.5)
	Pre-existing diabetes		4.1 (1.5-11.2)
	Chronic hypertension		2.8 (1.2-6.7)
	Alcohol use during pregnancy		2.1 (1.1-4.2)
NEUROBLASTOMA			
Case-Control Studies			
De Roos et al. 2001	Offspring with paternal occupational exposure (Unites States and Canada):		
	Self-reported exposure to TCE	22	1.4 (0.7-2.9)
	Industrial-hygiene-reviewed exposure	9	0.9 (0.3-2.5)

[a]Attenuation observed was due to greater rate of end-stage renal disease in exposed subjects in 1973-2000. Rate of disease increased in unexposed subjects in 2001 (sharp increase) and 2002 while rate in exposed subjects remained approximately constant.
Abbreviations: CI = confidence interval, OR = odds ratio, TCE = trichloroethylene.

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TABLE E-3b Studies of Neurologic Effects and Exposure to TCE

End Point	Reference	Population	TCE Exposure, Duration	Results
Neurobehavioral (measured with neurobehavioral core test battery with profile of mood states in addition to two tests of visual perception)	Reif et al. 2003	143 residents in vicinity of Rocky Mountain Arsenal, 1981-1986	Four exposure groups: <5 ppb, mean 20.6 years 5-10 ppb, mean 20.5 years 10-15 ppb, mean 18.8 years >15 ppb, mean 24.7 years	Adjusted mean neurobehavioral test scores about 10-20% lower in highest-exposure group than in lowest-exposure group; some evidence of greater depression, confusion, tension-anxiety in highest- exposure group than in lowest-expopsure group, but difference not statistically significant ($P = 0.08$, 0.14, 0.24, respectively); study found strong interaction between TCE exposure and alcohol consumption in induction of neurobehavioral deficits
Parkinson disease, parkinsonism	Gash et al. 2008	30 industrial co-workers with Parkinson disease, parkinsonism, chronic exposure to TCE	Exposure pathway assumed to be inhalation with some dermal absorption. Exposure level not reported. Mean duration: 27 yr Median duration: 28 yr	Three workers had diagnosis of Parkinson disease before study; 14 workers self-reported parkinsonian symptoms, 13 self-reported no symptoms (according to Unified Parkinson's Disease Rating Scale); asymptomatic group had significantly slower fine motor movement than control group ($P< 0.0001$), slightly faster hand movement than symptomatic group ($p < 0.01$)

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TABLE E-4 Studies of Cancer End Points and Exposure to PCE

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
BUCCAL CAVITY, PHARYNGEAL CANCER			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	19	0.55 (0.33-0.86) SIR
	Women	42	0.96 (0.69-1.29) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	10	1.1 (0.5-2.0) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	6	0.65 (0.50-0.83) SMR
	Women	10	0.71 (0.34-1.30) SMR
ESOPHAGEAL CANCER			
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	26	2.2 (1.5-3.3) SMR
	Little or no exposure	7	2.1 (0.9-4.4) SMR
	Medium-high exposure	16	2.2 (1.2-3.5) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Case-Control Studies			
Lynge et al. 2006	Nordic dry-cleaning workers	8	0.76 (0.34-1.69) RR
GASTRIC CANCER			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	56[a]	0.73 (0.55-0.95) SIR
	Women	135[a]	0.93 (0.78-1.09) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	20	0.9 (0.6-1.4) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	7	0.93 (0.37-1.91) SMR
	Women	24	1.11 (0.71-1.65) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	39	2.18 (0.97-4.89) MOR

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COLON CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	327[b]	0.86 (99%CI 0.74-0.99) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	60	1.2 (0.9-1.5) SMR
	Little or no exposure	28	1.1 (0.8-1.6) SMR
	Medium-high exposure	28	1.2 (0.4-1.5) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	3	0.65 (0.13-1.91) SMR
	Women	19	1.36 (0.82-2.13) SMR
	Employed <1 year (men and women)	12	1.33 SMR
	Employed 1-5 years (men and women)	3	0.85 SMR
	Employed >5 years (men and women)	4	2.94 SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	26[b]	0.83 (0.24-2.89) MOR
RECTAL CANCER			
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	15	1.3 (0.7-2.2) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.73 (0.08-2.65) SMR
	Women	13	1.67 (0.89-2.85) SMR
	Employed <1 year (men and women)	9	1.81 SMR
	Employed 1-5 years (men and women)	2	1.01 SMR
	Employed >5 years (men and women)	2	2.50 SMR
HEPATIC CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	28[c]	1.29 (99%CI 0.74-2.05) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	10	0.8 (0.4-1.5) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	53	2.57 (1.21-5.46) MOR
Lynge et al. 2006	Nordic dry-cleaning workers	11	0.76 (0.38-1.52) RR

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TABLE E-4 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
PANCREATIC CANCER			
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	28	1.1 (0.7-1.5) SMR
	Little or no exposure	14	1.2 (0.7-2.0) SMR
	Medium-high exposure	11	0.8 (0.4-1.5) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.49 (0.01-2.73) SMR
	Women	5	1.39 (0.45-3.25) SMR
	Employed <1 year (men and women)	2	0.91 SMR
	Employed 1-5 years (men and women)	2	2.15 SMR
	Employed >5 years (men and women)	1	2.22 SMR
Case-Control Studies			
Lynge et al. 2006	Nordic dry-cleaning workers	57	1.27 (0.90-1.80) RR
LARYNGEAL CANCER			
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	6	1.7 (0.6-3.7) SMR
	Little or no exposure	0	—
	Medium-high exposure	6	2.7 (1.0-5.8) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
LUNG CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	356[d]	0.71 (99%CI 0.61-0.81) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	20	0.94 (0.57-1.45) SIR
	Women	34	0.95 (0.66-1.33) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	125	1.4 (1.1-1.6) SMR
	Little or no exposure	34	1.0 (0.7-1.4) SMR
	Medium-high exposure	78	1.5 (1.2-1.9) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	13[e]	0.90 (0.48-1.53) SMR
	Women	25[e]	1.01 (0.65-1.49) SMR
Case-Control Studies			
Lee et al. 2003	Community downstream of electronics factory in Taiwan (chlorinated hydrocarbons; males)	41	1.75 (0.79-2.39) MOR

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BONE CANCER			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.61 (0.01-3.39) SIR
	Women	6	1.28 (0.47-2.78) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0[f]	—
	Women	4[f]	1.63 (0.44-4.18) SMR
	Employed <1 year (men and women)	2[f]	1.25 SMR
	Employed 1-5 years (men and women)	2[f]	3.23 SMR
	Employed >5 years (men and women)	0[f]	—
SOFT-TISSUE SARCOMA			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	3	1.4 (0.3-4.2) SIR
	Women	8	1.0 (0.4-2.0) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
BREAST CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water (women only)	536	1.09 (99%CI 0.97-1.21) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	0.00 (0.00-33.54) SIR
	Women	215	1.19 (1.03-1.36) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:		
	Little or no exposure	68	1.0 (0.8-1.3) SMR
	Medium-high exposure	30	0.8 (0.6-1.2) SMR
		29	1.2 (0.8-1.7) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	51	1.14 (0.85-1.51) SMR
	Employed <1 year (women)	31	1.08 SMR
	Employed 1-5 years (women)	14	1.25 SMR
	Employed >5 years (women)	6	1.32 SMR

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TABLE E-4 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
Case-Control Studies			
Aschengrau et al. 2003	Women with breast cancer in Cape Cod, MA, towns:[g]		
	≤ median exposure (latency 0-15 years)	377	0.9-1.5 OR
	> median exposure (latency 0-15 years)	402	1.1-1.4 OR
	> 75th percentile exposure (latency 0-15 years)	253	1.6-1.9 OR
	> 90th percentile exposure (latency 0-15 years)	90	1.3-1.9 OR
Vieira et al. 2005	Women with breast cancer in Cape Cod, MA, towns:		
	0-year latency:		
	Nonproxy subjects	101	1.1 (0.8-1.5) OR
	All subjects	155	1.1 (0.8-1.4) OR
	5-year latency		
	Nonproxy subjects	87	1.2 (0.9-1.8) OR
	All subjects	129	1.1 (0.9-1.6) OR
	7-year latency		
	Nonproxy subjects	71	1.1 (0.8-1.6) OR
	All subjects	111	1.1 (0.8-1.5) OR
	9-year latency		
	Nonproxy subjects	63	1.1 (0.7-1.6) OR
	All subjects	97	1.1 (0.8-1.5) OR
	11-year latency		
	Nonproxy subjects	49	1.1 (0.6-1.7) OR
	All subjects	79	1.2 (0.8-1.7) OR
	13-year latency		
	Nonproxy subjects	43	1.3 (0.7-2.1) OR
	All subjects	61	1.3 (0.9-2.0) OR
	15-year latency		
	Nonproxy subjects	30	1.4 (0.7-2.6) OR
	All subjects	44	1.4 (0.9-2.3) OR
	17-year latency		
	Nonproxy subjects	15	1.0 (0.4-2.2) OR
	All subjects	21	1.0 (0.6-2.0) OR
	19-year latency		
	Nonproxy subjects	6	1.1 (0.3-3.5) OR
	All subjects	9	1.1 (0.4-2.9) OR
CERVICAL CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	29	0.65 (99%CI 0.38-1.02) SIR

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Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):		
	Employed <1 year	177	1.1 (0.9-1.2) SIR
	Employed 1-5 years	69	1.1 (0.8-1.3) SIR
	Employed 5-10 years	26	1.6 (1.1-2.4) SIR
	Employed >10 years	1	0.1 (0.0-0.8) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	27	1.6 (1.0-2.3) SMR
	Little or no exposure	12	1.5 (0.8-2.7) SMR
	Medium-high exposure	11	1.4 (0.7-1.7) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):	21	0.80 (0.49-1.22) SMR
	Employed <1 year	14	0.84 SMR
	Employed 1-5 years	6	0.89 SMR
	Employed >5 years	1	0.34 SMR
Case-Control Studies			
Lynge et al. 2006	Nordic dry-cleaning workers	36	0.98 (0.65-1.47) RR
UTERINE CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	124	1.35 (99%CI 1.06-1.70) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE	337[h]	1.06 (0.95-1.18) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	15	1.1 (0.6-1.8) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (women):	5	0.91 (0.29-2.13) SMR
	Employed <1 year	3	0.88 SMR
	Employed 1-5 years	2	1.42 SMR
	Employed >5 years	0	—
OVARIAN CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	81	1.16 (99%CI 0.85-1.53) SIR
PROSTATIC CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	483	1.11 (99%CI 0.98-1.25) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	17	1.0 (0.6-1.6) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (men)	0	—

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TABLE E-4 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
TESTICULAR CANCER			
Cohort Studies—Incidence			
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE	1[i]	0.14 (0.00-0.76) SIR
Cohort Studies—Mortality			
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE (men)	0	—
RENAL CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	54	0.80 (99%CI 0.54-1.12) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	8[j]	1.06 (0.45-2.08) SIR
	Women	12[j]	1.09 (0.56-1.91) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	8	1.0 (0.4-2.0) SMR
	Little or no exposure	1	0.3 (<0.1-1.6) SMR
	Medium-high exposure	7	1.5 (0.6-3.1) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0[j]	—
	Women	3[j]	1.18 (0.24-3.44) SMR
	Employed <1 year	1[j]	0.62 SMR
	Employed 1-5 years	2[j]	3.08 SMR
	Employed >5 years	0[j]	—
Case-Control Studies			
Brüning et al. 2003	Hospital-based study in Arnsberg, Germany:		
	Self-reported exposure	7	1.64 (0.61-4.40) OR
	Self-reported narcotic symptoms	5	1.84 (0.57-5.96) OR
	Duration of self-reported exposure:		
	None	127	1 OR
	<10 years	4	2.46 (0.65-9.34) OR
	10+ years	3	1.02 (0.24-4.27) OR
Lynge et al. 2006	Nordic dry-cleaning workers	29	0.67 (0.43-1.05) RR
BLADDER CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	82	0.98 (99%CI 0.71-1.29) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO:	12	1.3 (0.7-2.4) SMR
	Little or no exposure	5	1.4 (0.4-3.2) SMR

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	Medium-high exposure	7	1.5 (0.6-3.1) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.96 (0.01-5.36) SIR
	Women	1	0.96 (0.01-5.33) SIR
Case-Control Studies			
Lynge et al. 2006	Nordic dry-cleaning workers:	93	1.44 (1.07-1.93) RR
	Employed 0-1 years	6	1.50 (0.57-3.96) RR
	Employed 2-4 years	10	2.39 (1.09-5.22) RR
	Employed 5-9 years	17	0.91 (0.52-1.59) RR
	Employed 10 years or more	53	1.57 (1.07-2.29) RR
SKIN MELANOMAS			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	137	1.42 (99%CI 1.13-1.77) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.48 (0.05-1.73) SIR
	Women	13	0.99 (0.53-1.69) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	4	0.8 (0.2-2.1) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	0	—
	Women	0	—
CENTRAL NERVOUS SYSTEM CANCER			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	37	1.54 (99%CI 0.96-2.31) SIR
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.40 (0.05-1.46) SIR
	Women	15	0.97 (0.54-1.61) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	5	0.6 (0.2-1.4) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	1	0.48 (0.01-2.66) SMR
	Women	6	0.91 (0.33-1.99) SMR
CENTRAL NERVOUS SYSTEM CANCER IN CHILDREN			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	6	1.05 (99%CI 0.24-2.70) SIR
LYMPHATIC AND HEMATOPOIETIC CANCER			
Cohort Studies—Incidence			

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TABLE E-4 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
Chang et al. 2005	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	6	0.73 (0.27-1.60) SIR
	Women	16	0.65 (0.37-1.05) SIR
Cohort Studies—Mortality			
MALIGNANT LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤ 9.1 ppm-year	16	1.1 (0.5-2.3) OR
	>9.1 to ≤78.8 ppm-year	13	1.0 (0.5-2.2) OR
	>78.8 ppm-year	2	3.4 (0.7-17.3) OR
NON-HODGKIN LYMPHOMA			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	111	1.09 (99%CI 0.84-1.38) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	12	0.9 (0.5-1.6) SMR
Case-Control Studies			
Lynge et al. 2006	Nordic dry-cleaning workers	42	0.95 (0.65-1.41) RR
Miligi et al. 2006	Cases with occupational exposure in Italy:		
	Very low-low	18	0.6 (0.3-1.2) OR
	Medium-high	14	1.2 (0.6-2.5) OR
	≤15 years	10	1.3 (0.5-3.3) OR
	>15 years	3	—
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	B-non-Hodgkin lymphoma:		
	>0 to ≤ 9.1 ppm-year	12	0.9 (0.4-2.0) OR
	>9.1 to ≤78.8 ppm-year	12	1.0 (0.5-2.3) OR
	>78.8 ppm-year	5	3.2 (0.6-16.7) OR
	T-non-Hodgkin lymphoma:		
	>0, ≤ 9.1 ppm-year	1	1.7 (0.2-14.4) OR
	>9.1 to ≤78.8 ppm-year	1	1.5 (0.2-12.5) OR
	>78.8 ppm-year	1	—
HODGKIN DIESASE			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE via drinking water	17	0.93 (99%CI 0.44-1.67) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	5	2.0 (0.6-4.6) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		

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	Men	0	—
	Women	1	2.23 (0.03-12.40) SMR
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤ 9.1 ppm-year	3	1.7 (0.4-6.9) OR
	>9.1 to ≤78.8 ppm-year	1	0.7 (0.1-6.3) OR
	>78.8 ppm-year	0	—
MULTIPLE MYELOMA			
Cohort Studies—Mortality			
Blair et al. 2003	Dry cleaners in St. Louis, MO	7	0.8 (0.3-1.6) SMR
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤ 9.1 ppm-year	3	1.8 (0.5-6.7) OR
	>9.1 to ≤78.8 ppm-year	0	—
	>78.8 ppm-year	0	—
LEUKEMIA			
Cohort Studies—Incidence			
Morgan and Cassady 2002	Redlands, CA, community exposed to TCE, PCE in drinking water	77[k]	1.02 (99%CI 0.74-1.35) SIR
Cohort Studies—Mortality			
Blair et al. 2003	Dry-cleaners in St. Louis, MO	12	0.8 (0.4-1.4) SMR
Chang et al. 2003	Electronics-manufacturing workers in Taiwan exposed to TCE, PCE:		
	Men	2	0.44 (0.05-1.59) SMR
	Women	8	0.54 (0.23-1.07) SMR
CHRONIC LYMPHOCYTIC LEUKEMIA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0, ≤ 9.1 ppm-year	1	—
	>9.1, ≤78.8 ppm-year	2	0.6 (0.1-2.8) OR
	>78.8 ppm-year	0	—
DIFFUSE LARGE B-CELL LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤ 9.1 ppm-year	3	0.9 (0.3-3.9) OR
	>9.1 to ≤78.8 ppm-year	6	2.1 (0.8-5.9) OR
	>78.8 ppm-year	1	2.3 (0.2-26.0) OR
FOLLICULAR LYMPHOMA			
Case-Control Studies			
Seidler et al. 2007	Cases with occupational exposure in Germany:		

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TABLE E-4 Continued

Reference	Study Population	No. Exposed Persons	MOR, OR, RR, SIR, or SMR (95% CI)
	>0 to ≤ 9.1 ppm-year	2	1.2 (0.3-5.5) OR
	>9.1 to ≤78.8 ppm-year	0	—
	>78.8 ppm-year	0	—
MARGINAL ZONE LYMPHOMA			
Seidler et al. 2007	Cases with occupational exposure in Germany:		
	>0 to ≤ 9.1 ppm-year	1	—
Costas et al. 2002	Cases in Woburn, MA (drinking water contaminated with TCE, PCE, other chemicals):		
	Ever exposed:		
	From 2 years before conception to case diagnosis	16	2.39 (0.54-10.59) OR
	During 2 years before conception	8	2.61 (0.47-14.37) OR
	During pregnancy	10	8.33 (0.73-94.67) OR
	From birth to diagnosis	12	1.18 (0.28-5.05) OR
	Cumulative exposure:		
	From 2 years before conception to case diagnosis:		
	Least exposed	9	5.00 (0.75-33.50) OR
	Most exposed	7	3.56 (0.51-24.78) OR
	During 2 years before conception:		
	Least exposed	4	2.48 (0.42-15.22) OR
	Most exposed	4	2.82 (0.30-26.42) OR
	During pregnancy:		
	Least exposed	3	3.53 (0.22-58.14) OR
	Most exposed	7	14.30 (0.92-224.52) OR
	From birth to diagnosis:		
	Least exposed	7	1.82 (0.31-10.84) OR
	Most exposed	5	0.90 (0.18-4.56) OR
Infante-Rivard et al. 2005	Maternal occupational exposure:		
	2 years before pregnancy up to birth		0.96 (0.41-2.25) OR
	During pregnancy		0.84 (0.30-2.34) OR

[a]Digestive organs and peritoneum.
[b]Colon and rectum.
[c]Results are for liver and biliary cancer combined.
[d]Lungs and bronchi.
[e]Trachea, bronchi, and lungs.
[f]Bone and articular cartilage.
[g]Combined data from present and previous study by Aschengrau et al. (1998).
[h]Female genital organs.

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[i]Testes and other male genital organs.
[j]Kidney and other unspecified urinary organs.
[k]All leukemias.
Abbreviations: CI = confidence interval, MOR = mortality odds ratio, OR = odds ratio, PCE = perchloroethylene, RR = relative risk, SIR = standardized incidence ratio, SMR = standardized mortality ratio, TCE = trichloroethylene.

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TABLE E-5a Studies of Noncancer End Points and Exposure to PCE

Reference	Study Population	No. Exposed Persons	OR (95% CI)
SYSTEMIC SCLEROSIS			
Case-Control Studies			
Garabrant et al. 2003	Women in Michigan, Ohio:		
	Self-reported exposure	7	1.4 (0.6-3.4)
	Expert-confirmed exposure	5	1.1 (0.4-2.9)
PRETERM LOSS			
Sonnefeld et al. 2001	Infants of Camp Lejeune residents, 1968-1985:		
	Exposure 1-3 weeks	14	1.0 (90% CI 0.6-1.6)
	Exposure 4-10 weeks	55	1.3 (90% CI 1.0-1.7)
	Exposure 11-20 weeks	86	1.3 (90% CI 1.1-1.6)
	Exposure >20 weeks, less than entire pregnancy	94	0.8 (90% CI 0.7-1.0)
	Exposure, entire pregnancy, less than 1 year before last menstrual period	158	1.1 (90% CI 0.9-1.3)
	Exposure entire pregnancy, at least 1 year before last menstrual period	36	0.8 (90% CI 0.6-1.1)
SMALL FOR GESTATIONAL WEIGHT			
Sonnefeld et al. 2001	Infants of Camp Lejeune residents, 1968-1985		
	Exposure 1-3 weeks	15	0.9 (90% CI 0.5-1.3)
	Exposure 4-10 weeks	60	1.1 (90% CI 0.9-1.4)
	Exposure 11-20 weeks	84	1.0 (90% CI 0.8-1.2)
	Exposure >20 weeks, less than entire pregnancy	16	1.2 (90% CI 1.0-1.4)
	Exposure entire pregnancy, less than 1 year before last menstrual period	207	1.2 (90% CI 1.0-1.3)
	Exposure entire pregnancy, at least 1 year before last menstrual period	61	1.1 (90% CI 0.9-1.4)
	All births	622	1.2 (90% CI 1.0-1.3)
	Mother's age <35 years	611	1.1 (90% CI 0.9-1.2)
	Mother's age ≥ 35 years	11	2.1 (90% CI 0.9-4.9)
	Mother had no previous fetal losses	475	1.1 (90% CI 0.9-1.2)
	Mother had one previous fetal loss	104	1.5 (90% CI 1.1-2.0)
	Mother had at least two previous fetal losses	43	2.5 (90% CI 1.5-4.3)
MEAN BIRTH WEIGHT			
Sonnenfeld et al. 2001	Infants of Camp Lejeune residents, 1968-1985		
	Exposure 1-3 weeks	189	Mean difference: 18 g (90% CI -40 to 76)
	Exposure 4-10 weeks	597	Mean difference: -17 g (90% CI -51 to 17)
	Exposure 11-20 weeks	915	Mean difference: -31 g (90% CI -59 to -3)
	Exposure >20 weeks, less than entire pregnancy	1,551	Mean difference: -28 g (90% CI -50 to -5)

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	Exposure entire pregnancy , less than 1 year before last menstrual period	1,994	Mean difference: -15 g (90% CI -35 to 5)
	Exposure entire pregnancy, at least 1 year before last menstrual period	605	Mean difference: -18 g (90% CI -51 to 16)
	All births	6,039	Mean difference: -26 g (90% CI -43 to -9)
	Mother's age <35 years	5,968	Mean difference: -2 g (90% CI -17 to 13)
	Mother's age ≥ 35 years	71	Mean difference: -130 g (90% CI -236 to -23)
	Mother had no previous fetal losses	4,985	Mean difference: -2 g (90% CI -17 to 13)
	Mother had one previous fetal loss	806	Mean difference: -16 g (90% CI -79 to 24)
	Mother had at least two previous fetal losses	245	Mean difference: -104 g (90% CI -174 to -34)
NEUROBLASTOMA			
Case-Control Studies			
De Roos et al. 2001	Offspring with paternal occupational exposure (Unites States, Canada)		
	Self-reported exposure to PCE	8	0.5 (0.2-1.4) OR
	Industrial-hygiene-reviewed exposure	4	0.5 (0.1-1.7) OR
SCHIZOPHRENIA			
Cohort Studies—Incidence			
Perrin et al. 2007	Offspring of dry cleaners in Jerusalem	4	3.4 (1.3-9.2) RR
NEUROBEHAVIORAL			
Cohort Studies			
Janulewicz et al. 2008 (Note: end point included two diagnoses—ADD and HD—and six indicators of learning disabilities)	Offspring of Cape Cod, MA, residents born 1969-1983	1,349	
	Prenatal exposure:	1,244	
	Low exposure		1.0-1.5 (0.7-2.7) OR
	High exposure		0.8-1.1 (0.4-1.6) OR
	Exposure 5 years postnatally:	1,326	
	Low exposure		0.9-1.4 (0.7-2.5) OR
	High exposure		0.6-1.0 (0.3-1.7) OR

Abbreviations: ADD = attention deficit disorder, CI = confidence interval, HD = hyperactivity disorder, OR = odds ratio, PCE = perchloroethylene.

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TABLE E-5b Visual Contrast Sensitivity and Visual Acuity

Reference	Population	Exposure, Duration	Effects
Schreiber et al. 2002	Apartment residents above dry cleaner	Mean, 778 µg/m^3 Median, 350 µg/m^3 Mean residence, 5.8 years Lifetime dose, 3,400 µg/m^3	Visual contrast sensitivity trend in Lanthony D15-d; no change in visual acuity
	Day-care workers sharing building with dry cleaner	Mean, 2,150 µg/m^3 Median, 2,150 µg/m^3 Mean work, 4.0 years Lifetime dose, 1,978 µg/m^3	Visual contrast sensitivity; no change in visual acuity

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