Exhibit 75

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene Exposure and Bladder Cancer Risk

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Abbreviations

1,1,1-TCA	1,1,1-Trichloroethane
ACS	American Cancer Society
AML	Acute Myelogenous Leukemia
ARRIVE	Animal Research: Reporting of *In Vivo* Experiments
ATS	Academy of Toxicological Sciences
ATSDR	Agency for Toxic Substances and Disease Registry
CI	Confidence Interval
CIR	Confidence Interval Ratio
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DCE	Dichloroethylene
DNA	Deoxyribonucleic Acid
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IOM	Institute of Medicine
JEM	Job-Exposure Matrix
JISA	Japan Industrial Safety Association
JTEM	Job Task Exposure Matrix
KCC	Key Characteristics of Carcinogens
MM	Multiple Myeloma
mmHg	Millimeter of Mercury
MNCL	Mononuclear Cell Leukemia
MTD	Maximum Tolerated Dose
MoA	Mode of Action
NAM	National Academy of Medicine
NASEM	National Academies of Sciences, Engineering, and Medicine
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NPTCC	Non-Papillary Transitional Cell Carcinoma
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OR	Odds Ratio
PCE	Perchloroethylene
PIR	Proportionate Incidence Ratio
PMR	Proportionate Mortality Ratio
ppb	Part per Billion
ppm	Parts per Million
PRR	Proportional Registration Ratio
PTCC	Papillary Transitional Cell Carcinoma
PVC	Polyvinyl Chloride

RR	Relative Risk
SciRAP	Science in Risk Assessment and Policy
SIR	Standardized Incidence Ratios
SMR	Standardized Mortality Ratio
SSA	Social Security Administration
TCA	Trichloroacetic Acid
TCC	Transitional Cell Carcinoma
TCOG	Trichloroethanol Glucuronide
TCOH	Trichloroethanol
TCC	Transitional Cell Carcinoma
TCE	Trichloroethylene
TVOC	Total Volatile Organic Compounds
US	United States
US EPA	United States Environmental Protection Agency
UTUC	Upper Tract Urothelial Carcinoma
U-TCA	Urinary Trichloroacetic Acid
VHA	Veterans Health Administration
VOC	Volatile Organic Compound

1 Overview

This report was prepared at the request of counsel for Defendants in *re: Camp Lejeune Water Litigation*, Case No.: 7:23-cv-897. The Plaintiffs claim that it is at least as likely as not that exposure to trichloroethylene (TCE), perchloroethylene (PCE), benzene, vinyl chloride, and *trans*-1,2-dichloroethylene (DCE) in water caused bladder cancer in individuals that worked or resided at Camp Lejeune.

I analyzed relevant epidemiology and toxicology literature to assess whether it supports a causal association between exposure to these chemicals and bladder cancer at Camp Lejeune or more generally. I considered study characteristics, quality, and results, and integrated epidemiology, toxicology, and mode-of-action (MoA) evidence using the Bradford Hill framework. My opinions are based on a review of the published scientific literature, including a substantial number of scientific and regulatory documents, as well as my training and experience in toxicology, epidemiology, and risk assessment.

Below, I provide an overview of my opinions regarding TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE exposure and bladder cancer at Camp Lejeune and more generally. My credentials are discussed in Section 2. After describing scientific principles and my methodology in Section 3, I provide an overview of carcinogenicity generally and bladder cancer specifically in Section 4. I review Camp Lejeune epidemiology studies in Section 5, and analyses of chemical-specific risks at Camp Lejeune again in subsequent sections to integrate them with the larger body of evidence on each specific chemical. Section 6 describes the epidemiology, toxicology, and MoA evidence regarding TCE and bladder cancer, and agency reviews of this evidence. I also evaluate the available evidence as a whole in the context of Bradford Hill's considerations. Similar information is provided in Sections 7, 8, and 9 for PCE, benzene, and vinyl chloride, respectively. In Section 10, I discuss available evidence for *trans*-1,2-DCE. I discuss mixtures toxicology in Section 11. My overall conclusions on all five chemicals and bladder cancer are presented in Section 12. Attachment A describes my literature search methods and Attachments B through K include tables with information on epidemiology and toxicity study quality, characteristics, and results. My *curriculum vitae* and testimony experience are provided in Attachments L and M, respectively.

1.1 Camp Lejeune Epidemiology Studies

Five studies have evaluated bladder cancer risks among Marines or Navy personnel stationed at Camp Lejeune or civilian workers on base. The methods used to assemble the study populations, characterize exposures, and address confounding varied across studies. Overall, there were no consistent associations reported between either working or living at Camp Lejeune, or TCE, PCE, benzene, or vinyl chloride exposures at Camp Lejeune, and bladder cancer. Almost all risk estimates were statistically null and close to 1. The few reported statistically significant risk estimates were not reported across other analyses of the Camp Lejeune population. These epidemiology studies also had several methodological limitations, including a high likelihood of exposure misclassification and the lack of adjustment for smoking in all studies except ATSDR (2018a), and the potential for selection bias in ATSDR (2018a). Also, NRC (2009) concluded that "limitations in population size, data availability, and data quality cannot be overcome." There are no animal carcinogenicity or mechanistic studies of Camp Lejeune drinking water, but animal carcinogenicity and mechanistic studies do not provide evidence that exposures to TCE, PCE, benzene, or vinyl chloride can cause bladder cancer.

Overall, (1) Camp Lejeune epidemiology studies are not of high quality, (2) most epidemiology analyses do not provide evidence of associations, and (3) animal and mechanistic studies do not provide evidence of causation in humans for TCE, PCE, benzene, or vinyl chloride. Thus, I conclude that the currently available evidence does not support a causal association between exposure to drinking water at Camp Lejeune generally or exposure to TCE, PCE, benzene, or vinyl chloride in drinking water at Camp Lejeune and bladder cancer.

1.2 TCE

TCE is a colorless, nonflammable, and volatile liquid. While there are a few circumstances in which TCE can occur naturally, it is most frequently manufactured for use as a solvent to remove greases, fats, tar, oils, and waxes and to make refrigerants, adhesives, paints, pesticides, lubricants, paint strippers, and varnishes for both industrial and commercial products. TCE has also been used by the textile processing and dry-cleaning industries. Impurities of commercially manufactured TCE include both PCE and 1,1,1-trichloroethane (1,1,1-TCA).

Individuals can be exposed to TCE from contaminated air, water, food, and soil. TCE can enter the body *via* inhalation, ingestion, and dermal contact. TCE has been found in prepared food at concentrations between 2 and 100 parts per billion (ppb). When TCE enters the body and reaches the bloodstream, most of it is quickly exhaled from the lungs. When TCE reaches the liver from the bloodstream, it is metabolized into breakdown products that are mostly excreted in the urine within 1 day. While repeated or high exposures to TCE can result in its storage in fat, once exposure has ceased, TCE and its breakdown products are rapidly released from fat. The half-life of TCE in the body is less than 3 days.

Although limited in quality (particularly with respect to a high likelihood of exposure misclassification and a lack of adjustment for potential confounders), most analyses do not provide evidence of associations between or exposure-response trends for TCE and bladder cancer in cohort and case-control studies. Animal evidence does not indicate that TCE can cause bladder cancer, and there is no proposed MoA with sufficient scientific support. I conclude that, as a whole, the currently available evidence does not support a causal association between TCE exposure and bladder cancer.

1.3 PCE

PCE, also known as PERC, perchloroethylene, or tetrachloroethylene, is a colorless, nonflammable, and volatile liquid. While it can occur naturally, PCE is most frequently manufactured for use as a solvent in the dry-cleaning, textile, automotive, and metal industries. It is used to remove grease and oil, repel water, and finish fabric; to manufacture other chemicals; and as an ingredient in some consumer products, including adhesives, degreasers, cleaners, lubricants, sealants, and polishes. PCE can degrade in the environment to TCE, and TCE may be present as a contaminant in products containing PCE.

Individuals can be exposed to PCE from contaminated air, water, food, and soil. PCE is one of the most commonly detected chemicals in indoor environments, due to its use in consumer products, building materials, and dry-cleaning products; its presence in drinking water; and its ability to vaporize. PCE can be absorbed into the body after inhalation, ingestion, or dermal contact. PCE is quickly absorbed into the bloodstream, and is quickly excreted *via* exhalation. PCE that is not quickly exhaled can be metabolized to breakdown products and excreted in the urine. PCE has an affinity for fat and can distribute to multiple organs, including the liver, kidney, brain, lung, and heart. The half-life of PCE in the body is about 3 days.

Although limited in quality (particularly with respect to a high likelihood of exposure misclassification and a lack of adjustment for potential confounders), most analyses do not provide evidence of associations between or exposure-response trends for PCE and bladder cancer in cohort and case-control studies. PCE did not cause bladder cancer in animal studies, and there is no proposed MoA with sufficient scientific support. I conclude that, as a whole, the currently available evidence does not support a causal association between PCE exposure and bladder cancer.

1.4 Benzene

At room temperature, benzene is a colorless, transparent liquid with a sweet odor. In the natural environment, benzene is emitted from volcanoes and forest fires and is present in crude oil. Benzene has been widely used in various industrial processes and as an additive to unleaded gasoline. Common anthropogenic sources of benzene exposure include tobacco smoke, automobile service stations, exhaust from motor vehicles, and industrial emissions. Automobile exhaust is the largest source of benzene in the environment. Benzene in indoor air is primarily associated with cigarette smoke. Because of its high volatility, benzene exposure mainly occurs *via* inhalation in the general population and in occupational settings.

Several epidemiology studies and a few animal bioassays have evaluated benzene exposure and bladder cancer. Most epidemiology studies reported risk estimates around 1, and statistically significantly increased associations were only reported in a few studies with indirect or non-specific exposure measurements. In addition, the epidemiology studies have critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. There is no evidence that benzene causes bladder cancer in animal models, and there is no evidence for a plausible MoA.

Although limited in quality (particularly with respect to a high likelihood of exposure misclassification and a lack of adjustment for potential confounders), most analyses do not provide evidence of associations between or exposure-response trends for benzene and bladder cancer in cohort or case-control studies. Animal evidence does not indicate that benzene can cause bladder cancer, and there is no proposed MoA with sufficient scientific support. I conclude that, as a whole, the currently available evidence does not support a causal association between benzene exposure and bladder cancer.

1.5 Vinyl Chloride

Vinyl chloride is a colorless, flammable gas with a mild, sweet odor that is unstable at high temperatures. It does not occur naturally. It can be formed when TCE, PCE, or trichloroethane break down in the environment. It is used almost exclusively to make polyvinyl chloride (PVC), which is used to make plastic products like pipes, wire and cable coatings, and packaging materials.

Small amounts of vinyl chloride can dissolve in water. Vinyl chloride in water or soil near the surface can evaporate, while vinyl chloride in air breaks down in a few days. Individuals can be exposed to vinyl chloride in air from cigarette and cigar smoke or near plastic manufacturing facilities, hazardous waste sites, and landfills. They can also be exposed to very low levels of vinyl chloride in drinking water. Workers can be exposed by breathing vinyl chloride in air or from contact with skin or eyes in the workplace.

Few studies have evaluated vinyl chloride exposure and bladder cancer. There is no evidence for a plausible MoA, and vinyl chloride does not cause bladder cancer in animal models. Most epidemiology studies reported risk estimates that were null and less than 1; statistically significantly increased associations were

only reported in a single study that relied on an indirect and non-specific exposure estimate. In addition, the epidemiology studies have critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding.

Although limited in quality (particularly with respect to a high likelihood of exposure misclassification and a lack of adjustment for potential confounders), most analyses do not provide evidence of associations between or exposure-response trends for vinyl chloride and bladder cancer in cohort or case-control studies. Animal evidence does not indicate that vinyl chloride can cause bladder cancer, and there is no proposed MoA with sufficient scientific support. I conclude that, as a whole, the currently available evidence does not support a causal association between vinyl chloride exposure and bladder cancer.

1.6 *trans*-1,2-DCE

DCE exists as 1,1-DCE and 1,2-DCE. *trans*-1,2-DCE was detected as a breakdown product of TCE in drinking water at Camp Lejeune. *trans*-1,2-DCE is a low molecular weight, volatile, halogenated liquid that is commonly used as a chemical intermediate or an industrial solvent. Most *trans*-1,2-DCE exposures are from anthropogenic sources. Specific industrial uses of *trans*-1,2-DCE include cleaning and degreasing, surface treatment, adhesion, spot cleaning, stain removal, and lubrication (US EPA, 2020b). Occupational exposure to *trans*-1,2-DCE most commonly occurs *via* inhalation or dermally, while the general population is exposed *via* inhalation or ingestion. The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and bladder cancer.

1.7 Agency Reviews

Chemical carcinogenicity is evaluated by government and scientific agencies, including ATSDR; the National Academies of Sciences, Engineering, and Medicine (NASEM); the United States Environmental Protection Agency (US EPA); the International Agency for Research on Cancer (IARC); and the National Toxicology Program (NTP). Despite the goal of being systematic and objective, all of their reviews involve some degree of subjectivity. In many instances, their reviews do not fully take study quality into account and therefore conclude that the strength of the evidence is stronger than it truly is. The IARC, US EPA, and NTP carcinogenicity categories all include "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding).

The review process for the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) has even more methodological issues than other reviews conducted by ATSDR and other agencies. ATSDR (2017a) did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation. Its conclusions regarding causation for many health outcomes are inconsistent with those of several other agency reviews, including other reviews by ATSDR.

Government and other agencies have either concluded that the scientific evidence is insufficient to make a determination regarding TCE and bladder cancer causation or have not drawn any conclusions. In the most recent reviews of the epidemiology evidence, most government and other agencies concluded there is some weak evidence for an association between PCE and bladder cancer, but that evidence is too limited to

support causation. Government and other agencies have either not reviewed the evidence for benzene and bladder cancer, have not drawn conclusions, or have concluded that there is inadequate or insufficient evidence to evaluate benzene and bladder cancer risk in humans. Most government and international agencies did not discuss bladder cancer in their reviews of vinyl chloride, while ATSDR (2017a) concluded there was "below equipoise evidence for [bladder cancer] causation" due to insufficient information. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to *trans*-1,2-dichloroethene…were located."

1.8 Conclusions

I did not identify any epidemiology studies of *trans*-1,2-DCE and bladder cancer. Many of the epidemiology studies are not of high quality and most analyses do not provide evidence of associations between TCE, PCE, benzene, or vinyl chloride exposure and bladder cancer. Animal carcinogenicity and mechanistic studies do not provide evidence of causation for these chemicals or *trans*-1,2-DCE. Based on the currently available evidence, I conclude, to a reasonable degree of scientific certainty, that TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE in Camp Lejeune drinking water did not cause bladder cancer.

2 Credentials

I am an epidemiologist and board-certified toxicologist with expertise in human health risk assessment. I am a fellow of both the American College of Epidemiology and the Academy of Toxicological Sciences (ATS), and I am currently on the Board of Directors of ATS. I am a Principal at Gradient, an environmental and risk sciences consulting firm. From 2009 to 2017, I was an adjunct faculty member in the Department of Epidemiology at the Harvard T.H. Chan School of Public Health.

I received an S.B. degree in environmental engineering science from the Massachusetts Institute of Technology in 1996. I received an Sc.M. in epidemiology and a Ph.D. in environmental health sciences/toxicology from the Johns Hopkins Bloomberg School of Public Health in 2000 and 2002, respectively. From 2002 to 2004, I was a Cancer Prevention Fellow at the National Cancer Institute (NCI), where I conducted several molecular epidemiology studies on colon, breast, and prostate cancers and was instrumental in the development of "Polymorphism Interaction Analysis," a statistical tool for cancer risk assessment. In 2004, I joined Gradient. My consulting practice consists of evaluating toxicity, epidemiology, and exposure data in the context of evaluating human health risks from substances in consumer products, pharmaceuticals, and medical devices, as well as from occupational and environmental exposures.

Based on my experience and expertise, I work with several organizations on issues relating to toxicology, epidemiology, risk assessment, and public health. Since 2008, I have served as an elected member of the Board of Health in Canton, Massachusetts, the community in which I reside. In this capacity, I provide advice on a broad range of public health topics, from the evaluation of chemical risks to the prevention of coronavirus disease 2019 (COVID-19). I am also a member of the Massachusetts Medical Reserve Corps and the Massachusetts Environmental Justice Assistance Network. In May 2012, I served as a panelist at a US EPA meeting that addressed how MoA evidence should be used in assessments of exposures to and health effects caused by chemical mixtures. In 2013, I served as an expert external peer reviewer for US EPA's "Provisional Peer-Reviewed Toxicity Values for Styrene-Acrylonitrile (SAN Trimer)" report. In 2014, I served as a reviewer for research grants submitted to the National Science Foundation, the California Breast Cancer Research Program, and the John Templeton Foundation. In 2016, I served as a reviewer for a K99 research grant submitted to the National Institute for Occupational Safety and Health. In 2017 and 2018, I served as a reviewer for several R21 research grants submitted to the National Institutes of Health.

I have been active in the Society of Toxicology for many years; I was previously the treasurer/secretary of the Risk Assessment Specialty Section and an elected member of the Nominating Committee. I am also active in the American College of Epidemiology, for which I served on the Board of Directors, and the Society for Risk Analysis. I taught "Research Synthesis and Meta-Analysis," a graduate-level course at the Harvard T.H. Chan School of Public Health. As reflected in my *curriculum vitae* (Attachment L), I have authored over 150 original peer-reviewed research articles, review articles (including systematic reviews, meta-analyses, and weight-of-evidence evaluations), and book chapters on a wide variety of chemicals, including TCE, PCE, and benzene, and health outcomes in peer-reviewed journals, books, and meeting proceedings. I was on the editorial boards of *Carcinogenesis* and *The Open Biomarkers Journal* and was a managing editor of the *Journal of Environmental Protection Science*. I have been a peer reviewer for more than 35 journals.

3 Principles and Methodology

I analyzed relevant epidemiology and toxicology literature, as well as agency reviews of this literature, to assess whether it supports a causal association between TCE, PCE, benzene, vinyl chloride, or *trans*-1,2-DCE exposure and bladder cancer. To conduct my analysis, I considered a number of well-established epidemiology and toxicology principles. These principles are described in this section, followed by a detailed discussion of my methodology, which includes a review of individual study quality and results, as well as an integration of study findings in the context of the Bradford Hill considerations (Hill, 1965; Garabrant, 2000).

3.1 Epidemiology

Epidemiology is the study of the causes, distribution, and control of disease in human populations (Lash *et al*., 2021). In epidemiology studies, both exposures and outcomes are measured or estimated, and statistical analyses are conducted to assess whether there are associations (*i.e.*, correlations) between the two. Unlike experimental animal studies, epidemiology studies involve exposure conditions relevant to humans. However, they sometimes involve very high exposures (*e.g*., in an occupational setting) that produce effects that would not be expected to occur at lower exposures (*e.g*., in the general population). Because these studies involve people living in the real world, study participants often have other exposures or attributes that make it difficult to determine whether an association is specific to the exposure of interest, and each epidemiology study can have other limitations that can affect the interpretation of its results. As such, associations in epidemiology studies do not always indicate causation, as they could be a result of chance, bias, or confounding.[1]

3.1.1 Risk Ratios

Epidemiology studies typically present risk ratios (often called risk estimates), including odds ratios (ORs), relative risks (RRs), standardized incidence ratios (SIRs), standardized mortality ratios (SMRs), hazard ratios (HRs), or incidence rate ratios (IRRs), depending on the study design. All are measurements or estimates of the rate of disease (*e.g.*, cancer) in people with an exposure of interest compared to the rate in unexposed people, as shown in the equation below:

$$\text{Risk Ratio} = \frac{\text{Rate of Disease in Exposed}}{\text{Rate of Disease in Unexposed}}$$

Definitions of these risk estimates are shown in Table 3.1.

[1] A confounder is associated with an exposure, but is not caused by that exposure, and can cause the disease of interest. Confounding bias can occur when a confounder is not fully accounted for in an analysis. For example, smoking is associated with alcohol consumption and can cause lung cancer. One might find an association between alcohol consumption and lung cancer because people who drink more alcohol smoke more, and not because drinking alcohol causes cancer.

Table 3.1 Risk Ratios

Risk Estimate	Definition
IRR	The ratio of the incidence rate of disease in the exposed group to the incidence rate of disease in the non-exposed group.
HR	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.
OR	The odds of disease in the exposed group divided by the odds of disease in the non-exposed group.
RR	The ratio of the risk in the exposed group to the risk of disease in the non-exposed group.
SIR	The number of people with a disease in a given population compared to what is "expected" based on the number of people with that disease in a reference population.
SMR	The number of people who die of a disease in a given population compared to what is "expected" based on the number of deaths due to that disease in a reference population.

Source: Lash *et al.* (2021).

If the rate of disease is the same in both exposed and unexposed people, then the risk ratio is 1, and there is no association between the exposure and disease. A risk ratio greater than 1 indicates there may be an increased risk for disease and a value below 1 indicates that those who are exposed have a lower risk for disease compared to those who are unexposed.[2]

A sample risk ratio on its own does not provide statistically meaningful evidence for the existence of an association between an exposure and a disease in the population. This is because, in a particular population of interest, a randomly selected study sample might not be representative of the population as a whole by chance, so the estimated risk ratio in the sample would not be representative of the true risk ratio in the population (Lash *et al.*, 2021; Ahlbom 1993). This would also be true if a sample was selected in a biased manner.

In epidemiology studies, a confidence interval (CI; typically, 95%) is often presented for the estimated measure of association (*e.g.*, risk ratio) to reflect uncertainties in the estimation due to random error. A 95% CI is derived to indicate a range of the sample risk ratio that has a 95% probability of capturing the true population risk ratio (Lash *et al.*, 2021; Ahlbom 1993). If a sample risk ratio's 95% CI does not contain 1, there is a 95% probability that the underlying population's risk ratio is different from 1, indicating that we can reasonably exclude chance as an explanation for the observed association (Naimi and Whitcomb, 2020). In contrast, if a sample risk ratio's 95% CI contains 1, one cannot confidently exclude the possibility that the underlying population's risk ratio is 1 (*i.e.*, there is no association) (Naimi and Whitcomb, 2020).

As noted by Savitz *et al.* (2024), "A correctly interpreted CI provides information about both the magnitude and precision of effects, indicating a range of possible parameter values that are statistically compatible with the data." This is because a CI reflects both the sample size of a study and the heterogeneity of the sample as reflected by the standard deviation or standard error of the effect being measured. The CI gives you some indication of the likelihood of the risk estimate being within a certain range with an acceptable amount of error (*e.g.*, a 95% CI reflects a willingness to be incorrect 5% of the time) (Lash *et al.* 2021).

The CI is not meaningful if it is based on a sample of the population that is not representative of the underlying population due to bias. The estimated risk from a biased or unrepresentative sample may not reflect the true risk in the underlying population and, while increasing the sample size of a study may result in increased precision, it may not reflect an increase in precision around the true effect estimate. That is, if

[2] SIRs are typically reported as a percentage (%) but are often converted to a value based on "1," similar to an RR or an OR (*e.g.*, 100% = 1).

the sample is biased or not representative of the underlying population, risk estimates for the population could be different, and may even occur outside of the original CI.

This is reflected in a relatively recent US EPA (2019) review, which stated:

> We recognized that results that failed to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted in this review observed associations with large effects sizes (*e.g.*, OR ≥ ~ 2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size or the potential for biases. Conversely, we also recognized that statistical significance does not necessarily imply clinical or biological importance, particularly with larger than necessary sample sizes and other study elements that influence the reliability of estimated effects.

Another metric that is often reported in epidemiology studies is the *p*-value, which is the probability of obtaining the observed test results, or more extreme results, assuming that the null hypothesis (*i.e.*, the supposition that there is no relationship between groups being measured) is correct (Lash *et al*., 2021; Ahlbom, 1993). A *p*-value less than 0.05 is often considered statistically significant (StatsDirect Ltd., 2020). If a *p*-value is less than 0.05, there is less than a 5% chance a study would have found an association between an exposure or other potential risk factor and a health outcome if they were truly unrelated, assuming the study is free from bias and confounding. However, similar to a 95% CI, the *p*-value cannot address whether an association is causal (Lash *et al*., 2021).

Both the 95% CI and the *p*-value are a function of sample size. That is, in some cases, a true association in a population will not be statistically significant (*e.g.*, the 95% CI includes 1 or the *p*-value is ≥ 0.05) because the sample is too small to detect it. For this reason, one cannot conclude with certainty that there is no association if a result is not statistically significant, only that the study does not provide evidence that there is an association. Conversely, a statistically significant result in a large sample may not reflect a true or clinically relevant difference at the population level (Lash *et al*., 2021). As noted by Stang and Rothman (2011), "No study is completely free of systematic error; thus, as confidence intervals shrink with increasing study size, they shrink around a value that is incorrect because of the systematic error. Consequently, as study size increases, confidence intervals become less likely to contain the truth, and *P*-values become small but irrelevant because they contain little information about where the truth lies." I also note that, while both the *p*-value and CI provide information on statistical significance, CIs provide more information on the precision of the estimate based on their widths (American Statistical Association, 2016).

Finally, Savitz *et al*. (2024) said, "Dichotomizing findings into 'significant' and 'not significant' reduces information, obscures biases, and often leads to misinterpreting strong associations as null and nearly identical results as conflicting." Savitz *et al*. (2024) instead suggest that one should always consider the full range of the CI, and if this range encompasses values below and above 1, one should conclude that it may support no association, a small association, or an increased risk depending on how wide this range is. Savitz *et al*. (2024) were, therefore, not opposed to testing statistical significance, but concluded that one should also consider the precision of effect estimates when interpreting results.

In this report, I consider not only statistical significance, but also the CI to get a sense of precision, and whether results are likely influenced by chance or bias, to determine how likely it is that there is an association in the population.

3.1.2 Study Design

There are several types of observational epidemiology study designs.[3] All epidemiology studies are likely subject to exposure and outcome misclassification, confounding, and bias to varying degrees. In some cases, the study limitations can be overcome with the study design (*e.g.*, matching in a case-control study to address confounding, or relying on medically confirmed disease outcomes instead of self-reported outcomes) or by using certain statistical methods (*e.g.*, adjusting for confounding). In other cases, study limitations cannot be overcome, and one must take them into account when interpreting a study's results. Below, I discuss some of the major strengths and limitations of several observational epidemiology study designs.

Cohort Studies

In prospective cohort studies, a cohort, or group of individuals who share a common characteristic (*e.g.*, birth year, place of residence, occupation) but are heterogeneous with regard to one or more exposures, is identified, and detailed information on cohort members' exposures of interest and other factors (*e.g.*, demographic factors, lifestyle factors, medical history, and health conditions) is obtained at enrollment. The cohort is then followed over time, and disease outcomes, and sometimes changes in exposure and other factors, are documented (Lash *et al*., 2021). Disease risks, incidence rates, or the time to disease occurrence in exposed and nonexposed individuals are then compared.

Prospective cohort studies are often considered to have the most robust observational epidemiology study design. In these studies, exposures of interest and characteristics of the cohort members are assessed at baseline and sometimes also during follow-up, before the occurrence of any disease. This prospective feature of exposure assessment protects risk factor data from recall bias (discussed below), which can occur in case-control studies. Extensive information on known or suspected risk factors for diseases of interest is often available for well-characterized cohorts, so the results generated from studies of these cohorts can be less biased when multiple potential confounders are considered in the statistical analysis, compared to case-control studies. However, unmeasured and residual confounding cannot be ruled out completely in any observational study. Although it is possible that people who choose to participate in a cohort study do not accurately reflect the population about which inferences are being made (which can bias the study's results), selection bias is less of a concern when a prospective cohort is assembled because a person's future disease status is unknown and thus cannot influence whether they participate in the study. In contrast, during the follow-up period, there can be issues related to the attrition of study participants (*i.e.*, loss to follow-up). If the loss to follow-up is related to either an exposure or the disease of interest, it can result in biased risk estimates. In addition, changes over time in exposures or other potential risk factors and in how diseases are defined or measured can impact the results of cohort studies (Gordis, 2014).

Retrospective cohort studies are generally conceived after a group of individuals have developed the disease of interest. In these studies, the investigators identify a point in time before these individuals developed the disease and assess their exposures at that point in time (or at several points in time), often by relying on historical records. Compared to prospective cohort studies, retrospective cohort studies are more prone to confounding because information on important risk factors for the disease of interest (*e.g.*, other chemical exposures) is often not available. Retrospective studies may also be prone to selection bias because participants are recruited after their exposure and disease status are known, and individuals' knowledge about their exposures and disease status may influence whether they participate (Gordis, 2014).

[3] In observational studies, the researchers observe the effects associated with an exposure, treatment, intervention, or other factor, but do not choose who is or is not exposed/treated. In contrast, in clinical and community trials, the researchers introduce a treatment or intervention and study associated effects (Gordis, 2014).

Case-Control Studies

In case-control studies, individuals with (cases) and without (controls) a specific disease are identified, and then each person's past exposures to a substance or substances of interest are measured or estimated (Paneth *et al.*, 2002). The control group is used to estimate the distribution of exposure in the source population that gives rise to the cases. Comparing the exposure distribution in the cases to that in the controls yields direct estimates of RR measures, such as ORs.

All case-control studies can suffer from bias, including selection and recall bias. Recall bias is a type of exposure misclassification error that occurs when study participants' ability to accurately recall past exposure is associated with their disease status (Sackett, 1979; Lash *et al*., 2009, 2021). In other words, diseased and non-diseased individuals may remember past exposures and events differently, leading to inaccurate estimates of associations between the exposure and the disease. Recall bias is not an issue in studies that use information that was collected before the disease diagnosis (*e.g*., from medical or occupational records). Selection bias occurs when an individual's probability of being included in a study is associated with exposure or disease status (Sackett, 1979; Lash *et al*., 2009). In a case-control study, selection bias can occur when investigators do not use the same criteria to select cases and controls, and when the criteria used are related to exposure status. Case-control studies are also vulnerable to selection bias related to nonresponse, when the decision to participate in a study is related to the case status and exposure experience, especially if the research hypothesis is known to the subjects. Case-control studies may also be subject to survivor bias if cases who have been cured or have died are excluded from the study.

Nested case-control studies and case-cohort studies are studies that are conducted within an established and often well-characterized cohort. In these studies, study participants are selected from the population of a larger cohort study, in which exposure information was collected prior to disease development. In a nested case-control study, controls are matched to cases based on follow-up time. In a case-cohort study, a sample of the total cohort is selected to be controls at baseline; however, these individuals may become cases during follow-up. Because the cases and controls are selected from the same source cohort in both nested case-control and case-cohort studies, the likelihood of selection bias is greatly diminished in studies using these designs compared to studies using the traditional case-control design (Lash *et al*., 2021). A unique advantage of nested case-control and case-cohort study designs is that the same subcohort can serve as a control population for different sets of cases (Lash *et al*., 2021).

Cross-Sectional Studies

In cross-sectional studies, individuals' exposure and disease status are ascertained at one point in time or over a short, defined period (Lash *et al*., 2021). In these studies, the prevalence of disease among exposed individuals is compared to the prevalence of disease among unexposed individuals. Although many exposures and diseases can be ascertained in a cross-sectional study, it cannot be known whether an exposure is causal, because exposure during the study period may differ from exposure prior to onset of the disease. Also, because one is studying prevalent cases (the current number of people with the condition) and not incident cases (the number of new cases with the condition who will be diagnosed over a given period), individuals who were cured or died prior to the study are not included, which could affect the study's results; this is known as survivor bias. Cross-sectional studies may also be subject to selection bias if those who participate in a study differ from those who do not.

Ecological Studies

Ecological studies examine aggregates of individuals defined by units (*e.g.*, geographic region, workplace) and assess whether the overall occurrence of disease in a population correlates with the overall occurrence

of exposure (Webster, 2007). There are no individual-level data in an ecological study, so it is not possible to know which specific individuals are exposed and which individuals have a disease. Thus, it is not possible to draw conclusions with certainty regarding whether exposure is a causal factor for the disease based on the results of these studies, and group-based associations between exposure and disease outcomes may not apply to individuals.

Semi-ecological or semi-individual studies assess outcomes, and sometimes covariates, at the individual level, but exposures are aggregated, so these studies also cannot provide evidence with respect to causation (Künzli and Tager, 1997). For example, some Camp Lejeune analyses are semi-ecological in that the exposure is aggregated (*i.e.*, employed or stationed at Camp Lejeune) while the outcomes are specific to each individual (*e.g.*, Bove 2024a, b).

Case Reports and Case Series

Case reports usually contain detailed information about individual patients. A case series is a group or series of case reports of individuals who had a similar health outcome or were given a similar treatment (Hennekens and Buring, 1987). Because there are no individuals without the outcome to consider for comparison in these studies, it is usually not possible to determine whether a particular exposure or treatment was a causal factor of the individuals' health outcomes.

Proportionate Mortality Studies

Proportionate mortality studies estimate the association between exposures to a chemical and a specific cause of death by comparing the proportion of deaths due to a specific cause in a group of individuals (*e.g.*, with a particular exposure) to the proportion in a comparison group in a proportionate mortality ratio (PMR) (Lash *et al*., 2021). These studies are often used to investigate the association between occupations and causes of death in large populations, and as such can be useful for rare diseases. However, these studies have significant methodological limitations (*e.g.*, the inability to determine whether an exposure is associated with an increase in a specific cause of death or a reduction of other causes of death; misclassification of the exposure or the cause of death). These studies cannot ascertain whether the exposure was a causal factor in the development of a fatal disease, and their results can be skewed based on other causes of death.

Pooled Analyses

A pooled analysis is a statistical analysis of individual data from primary studies (Blettner *et al*., 1999). A pooled analysis is often conducted to reconcile previous studies or may be prospectively planned, as part of the study protocol, to standardize data collection among several studies. With pooled analyses, new hypotheses may be examined, or different subgroups may be assessed, with the added sample size. Pooled analyses require that the original data characteristics be defined or planned prior to the evaluation. If similar data and models are available, heterogeneity among study populations, protocols, or results in a pooled analysis can be low. However, if heterogeneity within or among study populations, protocols, or results is high, pooled estimates may be difficult to interpret and are not appropriate to present (Blettner *et al*., 1999).

Systematic Reviews and Meta-Analyses

A systematic review evaluates a body of evidence using a systematic, reproducible, transparent approach that includes a research question, a search strategy, study inclusion and exclusion criteria, study screening methods, an evaluation of study quality, and information about data analysis and synthesis (Krnic Martinic *et al*., 2019). A meta-analysis is a type of systematic review that involves a statistical analysis of the results

of multiple independent studies, and generally aims to produce a single effect estimate (Egger *et al.*, 2001). Meta-analysis results are obtained in a two-stage process: first, a relevant summary statistic is obtained from each study; next, a weighted average is calculated. Study weights are chosen to reflect the amount of information each study contains. The number of subjects, risk of bias, and adjustment for confounders are often, but not always, considered in the assignment of weight. By statistically pooling the results from multiple studies, meta-analyses may allow for the detection of modest effects that were not observed in individual studies because of a lack of statistical power. They may also allow for the exclusion of small effects.

One issue with meta-analyses is that they may result in "over-conclusiveness," or the appearance that results are more precise and conclusive than they actually are (Lash *et al*., 2021). Also, because meta-analysis methods cannot correct the biases in the underlying study-specific results, these biases carry over to the meta-analysis results. When pooling studies with similar biases, individual study CIs and *p* values "tighten" to yield even stronger pooled values, resulting in this over-conclusiveness.

In addition, all systematic reviews and meta-analyses are subject to potential publication bias. Publication bias results when published research does not reflect the overall body of completed research studies. Typically, this occurs because journal editors are more likely to publish positive findings than null findings. As a result, the research literature becomes enriched in studies that report statistically significant results. Underrepresentation of null findings can bias the results of a systematic review or meta-analysis away from the null. One must carefully consider the issue of nonrandom sources of uncertainty when interpreting the results of systematic reviews and meta-analyses (Lash *et al*., 2021).

3.2 Toxicology

Toxicology is the study of the potentially adverse health effects of chemicals on living organisms (Hayes and Kobets, 2023). It encompasses studies of humans, laboratory animals, isolated cells, and isolated molecules, including MoA studies that assess how these chemicals may cause observed effects. An understanding of toxicology is necessary for determining to how much of a chemical one can be exposed, and under what conditions, without the likelihood of harm. In addition to an exposure assessment (*i.e.*, whether an individual had any contact with a chemical and, if so, to what degree and under what conditions, as discussed below), a determination of dose (the amount of a chemical taken into the body over time) is a key component of evaluating health effects from chemicals. Factors that may influence the toxicity of a chemical in individuals include genetic background, sex, age, health status, behavioral traits (*e.g.*, smoking and alcohol use), diet, and nutritional status (Aleksunes and Eaton, 2019).

The evaluation of the relationship between exposure to a chemical and health effects is referred to as a dose-response assessment. Although virtually every chemical can produce toxic (or adverse) effects at some dose, the range of doses necessary to produce adverse effects, injury, or death varies widely among chemicals (Aleksunes and Eaton, 2019; Faustman, 2019). The body has many biochemical and physiological processes that allow it to counteract a chemical's adverse effects, and most chemicals do not cause adverse effects unless the dose is sufficient to overwhelm the body's normal processes for a certain period of time. In other words, there is a threshold dose of most chemicals below which there is no evidence of adverse health effects (Clewell *et al*., 2019).[4]

The nature and severity of effects from a chemical can also vary with dose, and some chemicals that provide beneficial effects at low doses cause toxic effects at high doses. Aspirin, for example, provides pain relief

[4] In some cases, a threshold cannot be identified in scientific studies. The fact that a threshold cannot be identified does not mean that one does not exist.

at or below the recommended dose of two tablets per day, but increasingly higher doses of aspirin may cause adverse effects ranging from fever and acidosis to convulsions and respiratory failure (Ellenhorn and Barceloux, 1988; Grosser *et al*., 2011).

The frequency and duration of exposure to a chemical are also critical factors for determining its toxicity, and the adverse effects of a chemical can differ depending on whether exposure is to a single, large dose (acute exposure) or to lower doses over a long period of time (chronic exposure). For example, in the case of ethyl alcohol, acute exposure to a single dose can cause severe adverse effects in the central nervous system, whereas chronic exposure to lower doses can damage the liver and cardiovascular system (Bruckner *et al*., 2013). For most chemicals, acute exposures typically cause more severe health effects. With chronic exposure to sufficiently low doses, the body is able to eliminate each dose *via* excretion and repair any damage that may have occurred or adapt and find other means of accommodating each dose (Aleksunes and Eaton, 2019). Even if several individuals are exposed to a chemical at the same frequency and for the same duration, the severity of the adverse effects resulting from that exposure can vary because of differences in personal characteristics, as described above.

Finally, many chemicals can only affect tissues that they or their metabolites can physically access. The exposure route (*e.g*., ingestion, inhalation, and skin contact) and chemical and biological factors influence which tissues can be exposed to a chemical.

When animal studies are used to evaluate toxicity, study results must be extrapolated across species and often from relatively higher doses to the much lower concentrations to which humans may be exposed (US EPA, 2005a). For regulatory purposes, it is generally assumed that humans are as sensitive as the most sensitive animal species and that effects observed in animals can occur in humans, even though this is not always the case owing to differences in physiology and metabolism across species (US EPA, 2005a). This is because regulators do not estimate the likelihood of health effects actually occurring in a population or an individual (US EPA, 2004; ATSDR, 2018b). Rather, they use high-end estimates of exposure and toxicity (that generally result in overpredictions of potential health risks) to be protective of human health. That is, their aim is not to precisely define which health effects are expected to occur following an exposure, but to define the exposure level at which health effects are unlikely to occur (Aleksunes and Eaton, 2019).

For carcinogens, when an MoA for a particular chemical is not known, a linear approach is used for regulatory purposes to extrapolate risks at low doses from risks at high doses. A linear no-threshold (LNT) model assumes that there is no threshold exposure below which a chemical has no biological response. The LNT model also assumes that low doses over a lifetime will have the same effect as high doses over a short period of time. However, as stated by Clewell *et al*. (2019):

> Initial discovery that DNA mutation was the root of cancer led quickly to regulatory processes that assumed such a simple relationship could be described with a linear approach. This linear, no threshold approach has since become the default approach to risk assessment of chemicals with carcinogenic potential. Since then, a multitude of intrinsic processes have been identified at the molecular, cellular and organism level that work to prevent transient DNA damage from causing permanent mutations, and mutated cells from becoming cancer. Mounting evidence indicates that these protective mechanisms can prevent carcinogenesis at low doses of genotoxic chemicals, leading to non-linear dose-response. Further, a number of non-genotoxic mechanisms have demonstrated threshold-shaped dose-response for cancer outcomes

The LNT model provides a conservative estimate of risk that is public-health protective (US EPA, 2005), and that overestimates cancer risks at low doses.

3.3 Individual Study Reviews

I conducted a systematic review of the relevant epidemiology and animal carcinogenicity studies of bladder cancer. First, I reviewed government and other agency assessments of TCE, PCE, benzene, vinyl chloride, and *trans*-1,2,-DCE to identify epidemiology and animal carcinogenicity studies that evaluated exposure to these chemicals and bladder cancer for various purposes. I also conducted literature searches using PubMed and Scopus for studies published after these assessments' literature searches were completed and reviewed the reference lists of identified studies to find additional relevant studies (Attachment A).

For all of the epidemiology and animal carcinogenicity studies included in my evaluation, I summarized relevant information on study characteristics and results, as well as study quality, in text and tables. With the exception of studies of Camp Lejeune populations, all of which I have reviewed here, if several epidemiology studies analyzed the same cohorts or population groups, I generally summarized only the most recent study (because it had longer follow-up times and/or used more reliable exposure estimates), unless older studies reported additional results (*e.g.*, dose-response relationships). I excluded studies that examined non-specific aggregations of chemical exposures (*e.g.*, solvents, hydrocarbons) or that evaluated exposures to chemicals in ambient air.[5] Finally, because some epidemiology study designs are inherently lower in quality and limited in terms of the information that they can provide regarding causal inference (*e.g.*, case reports, ecological studies, PMR studies), I only conducted formal quality assessments and detailed reviews of cohort and case-control studies. For animal carcinogenicity studies, I focused on chronic toxicity studies, because acute, subacute, and subchronic studies do not observe animals for a long enough duration to be able to evaluate the development of tumors.

I evaluated the quality of the epidemiology and animal carcinogenicity studies to determine how valid and reliable the results of individual studies are for addressing causation. The study quality criteria I used are based on those identified from several available frameworks (*e.g.*, reviewed by Lynch *et al*. [2016] and Waspe *et al*. [2021]). Although aspects of these frameworks differ, they all share common themes. For each individual epidemiology and animal carcinogenicity study, I assessed strengths and limitations for each critical quality aspect presented in Sections 3.3.1 and 3.3.2, respectively, but I focused on those aspects that were most likely to impact the validity and reliability of each study's results.

I focused my in-depth systematic review on epidemiology and animal carcinogenicity studies because these studies provide the most direct evidence for the potential of a particular agent to cause cancer. I also conducted a high-level review of available *in vitro* and *in vivo* mechanistic studies, with a specific focus on those studies that have been proposed to support specific mechanisms by which TCE, PCE, benzene, vinyl chloride, or and *trans*-1,2,-DCE could cause bladder cancer. For these studies, I reviewed the results to determine whether they are sufficient to support a MoA for cancer, considering important factors such as assay type and the overall relevance of the results within the context of the treatment (*i.e.*, dose, route, and duration) and model system (human, non-human mammalian, non-mammalian).

Camp Lejeune epidemiology studies are reviewed in Section 5. TCE, PCE, benzene, and vinyl chloride epidemiology studies are reviewed in Sections 6.1, 7.1, 8.1, and 9.1, respectively, and TCE, PCE, benzene, and vinyl chloride animal carcinogenicity and mechanistic studies are reviewed in Sections 6.2, 7.2, 8.2, and 9.2, respectively. I reviewed the limited evidence for *trans*-1,2-DCE in Section 10.

[5] As noted by ATSDR (2024), which also excluded epidemiology studies of benzene exposures in ambient air, there is "great uncertainty about causality in these studies." The agency further stated, "Major uncertainty in the interpretation of these ambient exposure studies is that benzene levels (air or biomarkers) may have been a surrogate variable for exposure to 'air pollution' in general (*e.g.*, emissions from fuels and fuel combustion). These pollutants (*e.g.*, BTEX, NO2, PM10) tend to be correlated."

3.3.1 Epidemiology Studies

As summarized in Table 3.2, the quality domains I considered for epidemiology studies are the study population, exposure assessment, outcome assessment, covariates considered, and temporality. Following the table, I describe in detail the key aspects of each domain and how differences in the design or execution of these key aspects can impact the quality of an epidemiology study. I consider all of these domains for each study reviewed in detail in the attachments to this report, but as suggested by Savitz *et al*. (2019), I focus my discussion on the few critical aspects that warranted detailed assessment based on their potential impact on a study's validity and reliability. For most of the epidemiology studies I reviewed, the exposure assessment is the factor most likely to critically impact the validity of results. This is because most environmental epidemiology studies do not use robust quantitative methods for estimating exposure (*i.e*., direct measurements), although some use semiquantitative methods that are more reliable than studies that use strictly qualitative methods.

Table 3.2 Epidemiology Study Quality Evaluation Criteria

Parameter	Strength	Weakness
Study Population	▪ Appropriate study and comparison groups (cohort study) or case and control selection (case-control study) ▪ ≤20% loss to follow-up/excluded or >80% enrollment ▪ Nondifferential participation rates (≤15% difference in rates between cases and controls in case-control study)	▪ Inappropriate study and comparison groups (cohort study) or case and control selection (case-control study) ▪ >20% or unknown percentage of loss to follow-up/excluded, ≤80% or unknown percentages of enrollment/participation ▪ Differential participation rates between cases and controls (>15% difference in rates between cases and controls in case-control study)
Exposure Assessment	▪ Direct chemical exposure measurement ▪ Quantitative or semiquantitative exposure estimate (*i.e.*, duration, frequency, or intensity) ▪ ≤5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Assessed the time-varying nature of exposure	▪ Indirect chemical exposure measurement (*e.g.*, job history or self-reported exposure) ▪ Qualitative exposure estimate (*e.g.*, ever/never, job title) ▪ >5% missing data that are not addressed, or amount of missing data unknown ▪ Did not assess the time-varying nature of exposure ▪ Exposure information ascertained after outcome occurred
Outcome Assessment	▪ Cases/deaths identified or validated using reliable source (*e.g.*, registry, hospital records) ▪ Assessed disease incidence ▪ ≥5 years of follow-up	▪ Assessed disease mortality only ▪ Unconfirmed self- or proxy-reported outcome ▪ <5 years of follow-up
Covariates Considered	▪ Controlled for or considered age, sex, race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, a personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ ≤5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Considered time-varying nature of relevant covariates	▪ Did not control for or consider age, sex, race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, a personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ >5% or unknown amount of missing data that were not appropriately addressed ▪ Did not consider time-varying nature of relevant covariates
Temporality	▪ Exposure measured or documented before the outcome ▪ Appropriate consideration of latency (lag ≥4 years or exclusion of cases occurring ≤4 years after exposure)	▪ Exposure not measured or documented before the outcome ▪ No/insufficient consideration of latency (<4 years)

Notes:
JEM = Job-Exposure Matrix; MICE = Multiple Imputation Chained Equations.

Study Population

Selection bias is introduced when the individuals, groups, or data in an analysis are chosen in such a way that they may not be representative of the population about which researchers are making inferences. I considered cohort studies that have higher rates of enrollment or retention (>80%) (Kristman *et al.*, 2004)

and case-control studies with nondifferential participation rates (*i.e.*, participation rates in cases and controls differ by at most 15%) to be less likely to be subject to selection bias (Gordis, 2014).[6] If a study recruited or retained participants that systematically differ from the population of interest (*e.g.*, when recruited from hospitals), or if the exposed and unexposed (cohort study) or diseased and non-diseased (case-control study) differ on important factors, risk estimates may be biased (Gordis, 2014).

Exposure Assessment

In epidemiology studies, chemical exposures are commonly estimated using job titles, job-exposure matrices (JEMs) in which exposures are linked to occupational titles or tasks by experts, air or water monitoring or modeling, biomarkers (including exhaled breath and urine metabolites), self-reported exposures, or residential proximity to chemically contaminated sites.

I considered personal or occupational monitoring with sufficient information regarding time spent near the monitor to be the strongest methods for measuring exposure. I considered other means of estimating exposure, including job titles, JEMs, biomarkers (including exhaled breath and urine metabolites), self-reported exposures, the presence of a chemical in drinking water (either measured or modeled), and residential proximity to contaminated sites, to be weaker methodologically because of the higher likelihood of misclassification. However, among these latter methods, those that are applied in a quantitative or semi-quantitative manner (*i.e.*, those that consider duration, frequency, or intensity of exposure) are stronger than those that are qualitative (*e.g.*, those that evaluate ever *vs.* never exposed or exposure based on job title).[7] For example, those based on JEMs with some chemical measurement data or modeled drinking water concentrations (without water consumption data) based on chemical measurements are more reliable than other methods that lack any quantitative basis for exposure estimates.

While JEMs provide an indirect measurement of exposure, they are often more reliable than qualitative methods of estimating exposure (*i.e.*, ever *vs.* never exposed, or job title), but the quality of an exposure assessment based on a JEM varies based on the expertise of the person or people linking job titles to exposures, and whether the assessment is semiquantitative or not (*e.g.*, whether the duration, frequency, or intensity of exposure is considered). Also, exposure estimates based solely on job titles are subject to potential exposure misclassification due to possible differences in tasks and exposure conditions for specific jobs. Using these (or other) broad categories for exposure assessments also does not account for individual job characteristics that could modify an individual's exposure potential. They also usually do not account for differences in chemical exposures in terms of the exposure route, duration, frequency, or intensity. I considered studies that estimated duration of exposure to a chemical by duration of employment, or by using information from self-reported work history, census data, or company records as proxies for exposure dose, to be of higher quality than those that did not, but these exposure estimates are still subject to the same issues discussed above, including misclassification and recall inaccuracies. Overall, estimated chemical exposure concentrations in studies that relied on JEMs or job titles more generally do not always reflect actual individual exposure levels, but are more likely to be accurate when they are based on chemical measurements.

Directly measured or modeled chemical concentrations in the environment (*e.g.*, drinking water) are more reliable than exposure estimates that are not based on any quantitative information, but with no direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption

[6] I am not aware of any standard cutoff, so I considered a >15% difference in participation rates between cases and controls to constitute differential participation.

[7] Duration of employment is often used in studies as a proxy for exposure. However, intensity and frequency of exposure could vary dramatically over the same duration of time for different people. For example, an individual who was exposed to consistent high levels of TCE daily over 10 years would be in the same exposure category as someone exposed to intermittent low levels of TCE for 10 years, despite having very different cumulative exposure profiles.

data), neither type of estimate is likely to be accurate and reliable with respect to individual exposures. In contrast, direct measurements of chemical concentrations in the environment (*e.g.*, drinking water) that are linked to robust individual exposure data (*e.g.*, water consumption data) can provide reliable and accurate direct exposure information. Modeled chemical concentrations in the environment (*e.g.*, in drinking water) based on chemical measurements in the environment (*e.g.*, groundwater) could similarly provide high-quality exposure data when linked to individual exposure data (*e.g.*, water consumption data); however, the quality and accuracy of estimates of modeled chemical concentrations depend on the accuracy of the model's assumptions. In addition, chemical concentration measurements or estimates in the environment that reflect contamination levels at only a single or a few points in time do not necessarily reflect long-term exposure concentrations. Also, studies that provide estimates of exposure for aggregated chemicals (*e.g.*, all chlorinated hydrocarbons) or chemicals that are highly correlated (*e.g.*, categorized TCE, benzene, vinyl chloride and TVOCs in some Camp Lejeune studies), or studies where co-exposures to other chemicals are known to occur but are not controlled for in the analysis, are of lower quality than studies that estimate exposures to individual chemicals if the goal of the study is to estimate risks of particular chemicals. This is not the case if one is interested in determining the risk of a mixture (*i.e.*, if one is interested in the risk of drinking water at Camp Lejeune, one only needs to assess exposure to drinking water).

Biomonitoring can provide high-quality exposure measurements in epidemiology studies, particularly when risks from recent exposures are of interest or if exposures were relatively constant over an extended period of time. However, biomonitoring does not provide accurate estimates of past exposures when measured chemicals or metabolites reflect only recent or non-specific exposures. As described below, biomarkers for the volatile organic compounds (VOCs) at issue in this matter are not robust measures of exposure.

- TCE and PCE are rapidly absorbed into the bloodstream and are quickly excreted *via* exhalation (ATSDR, 2019b; US EPA, 2011, 2012). TCE and PCE that are not quickly exhaled can be metabolized to breakdown products and excreted in the urine (ATSDR, 2019b; US EPA, 2011, 2012). Trichloroacetic acid (TCA) is a metabolite of TCE, PCE, and other chlorinated hydrocarbons, and can be measured in blood and urine, but it is not specific and only represents recent exposure (IARC, 2014a; Cichocki *et al*., 2016; ATSDR, 2019b). As a result, it is generally not feasible to measure long-term TCE or PCE exposure using biomonitoring.
- Benzene and several benzene metabolites can be measured in urine, but the only benzene-specific metabolite is S-phenylmercapturic acid (Arnold *et al*., 2010). Benzene can also be detected in blood as a marker of recent exposure (CDC, 2017). Smoking and exposures to gasoline and petroleum products can result in higher concentrations of benzene in blood (CDC, 2017), so it can be difficult to assess exposures to a specific source of benzene exposure if these other factors are not well controlled for.
- Vinyl chloride can be measured in exhaled breath but is of limited use for biomonitoring because it is only an indicator of recent exposure. Thiodiglycolic acid and N-acetyl-S-(2-hydroxyethyl)-cysteine are metabolites of vinyl chloride in urine but they are not specific, so they have limited utility for biomonitoring (ATSDR, 2024a).

With respect to missing data, I found that studies that were missing exposure data on <5% of the study population or that used appropriate analytical methods to address the missing exposure data (*e.g.*, multiple imputation) are stronger than studies that had ≥5% missing data and did not account for missing data with appropriate methods (Jakobsen *et al*., 2017; Perkins *et al*., 2018).

Finally, self-reported exposure information is subject to potential recall inaccuracy, particularly when there are long time periods between exposures and study participant interviews. It is also subject to bias, particularly in case-control studies, when cases and controls may systematically recall prior exposures differently.

Outcome Assessment

I determined that studies that included a diagnosis or confirmation of bladder cancer by a medical professional or a histological evaluation, or that included bladder cancer cases identified from a disease registry, provide stronger outcome data than studies that relied on self- or proxy-reports of bladder cancer, because the latter are more likely to be subject to misclassification.

Because bladder cancer is not always fatal and fatality rates have changed over time, and because data from death certificates are not always reliable (*e.g.*, contributing causes of death are not always reported), I considered studies that only evaluated bladder cancer mortality to be weaker than those that evaluated bladder cancer incidence (NCI, 2024a; McGivern *et al.*, 2017).

I considered cohort studies that followed participants for a long enough duration (≥5 years) to be able to capture a sufficient number of disease cases for analysis, particularly for rare outcomes, to be stronger.

Covariates

A covariate is an independent variable that can influence the outcome of interest, but that is not of direct interest itself; it may be a confounder but does not have to be (Porta, 2014). Age, sex, race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, a personal or family history of bladder cancer, and genetics are risk factors for bladder cancer (Mayo Clinic, 2017; ACS, 2014). Smoking, in particular, has been estimated to cause about half of all bladder cancers (ACS, 2024). All of these factors should be considered as covariates in studies of bladder cancer, even if they are not confounders, because including them in statistical models increases the precision of effect estimates without increasing bias (Quintiles Outcome, 2013). I therefore considered studies to be stronger if they controlled for at least some of these factors in the study design or analysis.

There is some evidence that certain medications or dietary factors may be associated with bladder cancer, including the diabetes drug pioglitazone, aristolochic acid containing supplements, and arsenic in drinking water, while fluid intake is inversely associated with bladder cancer (ACS, 2024). Studies in specific populations should consider these factors (*e.g.*, populations with high prevalence of diabetes should consider pioglitazone exposure). Because certain industrial occupations involve exposures to a variety of chemicals, including solvents, I deemed studies that considered the potential for exposure to several chemicals in their analyses stronger than those that did not.

Studies that assessed covariates that can vary over time (*e.g.,* smoking) and considered changes over time in their analyses are stronger than studies that only assessed these covariates at a single time point. Studies with <5% missing covariate data or that used appropriate analytical methods to address missing data (*e.g.*, imputation) are stronger than studies with ≥5% missing data that did not account for missing data with appropriate methods (Jakobsen *et al.*, 2017; Perkins *et al.*, 2018).

Temporality

I considered studies that measured or documented exposures prior to diagnoses to be of higher quality than those that measured or documented exposures at the time of or after diagnoses, because the former are more likely to have appropriately captured the temporal relationship between the exposure and the outcome (Gordis, 2014). Similarly, studies that incorporated a lag (either by design or in their analysis) in the time between the exposure and the outcome are stronger than studies that did not, particularly considering the latency period for cancer. Studies with an insufficient duration of time between the exposure and bladder

cancer development (<4 years) (CDC, 2015) are weaker than those with sufficient time between the exposure and bladder cancer development (≥4 years). While this period of time might not be sufficient for cancer to develop, I felt it was appropriate, as it allowed me to err on the side of overestimating quality.

3.3.2 Toxicology Studies

3.3.2.1 Animal Carcinogenicity Studies

Studies in rodents can be classified based on their duration as acute (less than 24 hours), subacute (24 hours - <1 month, although most last 28 days), subchronic (1-3 months, although most last 13 weeks), and chronic (typically 6 months to 2 years) (Aleksunes and Eaton, 2019; OECD, 2024). I focused my analysis on chronic studies because those with shorter durations may not be sufficient for cancers to develop. I discuss subchronic studies only if they are the basis of any agency conclusions.

I assessed animal carcinogenicity study strengths and weaknesses based on several formal quality and risk-of-bias frameworks, including the Integrated Risk Information System (IRIS) (US EPA, 2022; NRC, 2014), NTP Office of Health Assessment and Translation (OHAT) (NTP, 2019), Science in Risk Assessment and Policy (SciRAP) (Molander *et al*., 2014), and "Animal Research: Reporting of *In Vivo* Experiments" (ARRIVE) (Percie du Sert *et al*., 2020; Batke *et al*., 2023) frameworks. I also considered whether the studies were consistent with the Organisation for Economic Co-operation and Development (OECD) "Guidelines for the Testing of Chemicals" (OECD, 2024) (referred to hereafter as the OECD Guidelines).

In Table 3.3, I summarize the key aspects of the quality domains I considered for animal carcinogenicity studies: reporting, allocation, bias, sample, chemical administration and characterization, exposure conditions, and outcome evaluation. I considered all of these factors in detail in the attachments to this report, but only those factors that are likely to have a considerable impact on the validity and reliability of a study's results are discussed in the text. For most of the animal carcinogenicity studies, the background tumor rate, the general health of the study animals, and the observation period can have the biggest impact on the reliability of their results. If the study animals have a high background cancer rate, are generally unhealthy, or are observed over their lifespan, it is more likely that cancers observed following an exposure are not related to that exposure.

Table 3.3 Animal Carcinogenicity Study Quality Evaluation Criteria

Parameter	Strength	Weakness
Reporting	For each outcome, report: (1) animal species; (2) test article name; (3) experimental design; (4) levels, duration, and route of exposure; (5) outcome evaluation methods; and (6) qualitative or quantitative results.	Do not report all these aspects.
Allocation	Random allocation of animals to experimental groups.	Do not specify whether allocation to experimental groups was random.
Bias	No indication that there were differences across treatment groups that could bias results (*e.g.*, co-exposures, vehicle, diet, gavage error, palatability, husbandry, health status).	Variables not adequately balanced across experimental groups, potentially biasing the results.
Sample	Adequate sample size; all animals were accounted for throughout the study.	Inadequate sample size; animals not all accounted for throughout the study.
Chemical Administration and Characterization	Chemical source, purity, and composition were adequate, chemical purity was independently verified, and steps were taken to ensure reported exposure levels were accurate.	Chemical source, purity, or composition were inadequate, chemical purity was not independently verified, or no steps were taken to ensure reported exposure levels were accurate.
Exposure Conditions	Several doses were tested, tested doses were below levels that can cause early mortality (unless early mortality was caused by the health outcome of interest), and the duration of exposure was appropriate for assessing the outcome of interest.	Only one dose tested, tested doses were too high and caused early mortality not caused by the health outcome of interest, or the duration of exposure was inappropriate for assessing the outcome of interest.
Outcome Evaluation	Valid, reliable, sensitive, and specific outcome evaluation method and appropriate observation period.	Invalid, unreliable, insensitive, or nonspecific outcome evaluation method or inappropriate observation period.

Note:
These criteria are based on the Integrated Risk Information System (IRIS) (US EPA, 2022; NRC, 2014), National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) (NTP, 2019), Science in Risk Assessment and Policy (SciRAP) (Molander *et al.*, 2014), and "Animal Research: Reporting of *In Vivo* Experiments" (ARRIVE) (Percie du Sert *et al.*, 2020; Batke *et al.*, 2023) study quality/risk-of-bias frameworks.

Reporting

I considered studies to be stronger if they clearly reported the species and strain of animals; the identity, source, and purity of the test chemical; the experimental design; the levels, duration, timing, frequency, and route of exposure; the outcome evaluation method; and qualitative and quantitative results for all the outcomes outlined in the methods of the study report or article. I assessed whether a study's reporting was adequate by considering whether all the elements of the study are described well enough that the study could be reproduced, and whether the methodological rigor and reliability of the authors' conclusions can be evaluated (US EPA, 2022).

Allocation

I determined that studies that randomly allocated animals to experimental groups are stronger than those that did not, as random allocation helps to minimize selection bias and systematic differences in animals among treatment groups. Employing appropriate randomization techniques ensures that each animal has an equal chance of receiving a particular treatment. Merely selecting an animal "at random," based on arbitrary judgment, does not constitute statistical randomization. Ideal methods for randomization include weight randomization or utilizing random number generators. Studies that did not randomize animals are more prone to reporting exaggerated results that meet conventional statistical significance thresholds (Percie du Sert *et al*., 2020; Batke *et al*., 2023; Haseman, 1984).

Bias

Bias refers to a systematic error or deviation from the truth in a study's results or in the interpretation of its results, potentially leading to an inaccurate estimation of the true effect. The impact of bias can range from trivial to substantial, with the latter resulting in a finding that may be completely attributed to bias (Percie du Sert *et al*., 2020). Often the impact of a bias on study results is unknown, making the interpretation of study results difficult. Common types of bias include selection bias, performance bias, detection bias, and attrition bias.

In animal carcinogenicity studies, factors such as co-exposures to multiple chemicals, diet, palatability, and husbandry practices (*e.g*., light-dark cycles, caging variables) can contribute to variability within groups. I considered stronger studies to be those that reported the strategies taken to mitigate potential discrepancies between treatment groups throughout the entire experimental period and lower-quality studies to either have differences between treatment groups or a lack of sufficient information to enable a reliable assessment of bias.

Sample

I considered stronger studies to be those that specified the exact number of experimental animals allocated to each treatment group, the total number of animals in each experiment, and the total number of animals used in the entire study. This information is critical when assessing the validity of a study's statistical analyses and the reliability of its experimental results. It is also preferable for studies to justify how the sample size was chosen, and to ensure the bioassay has sufficient statistical power (Percie du Sert *et al*., 2020). The appropriate sample size also depends on the endpoint being studied. For carcinogenicity assays, the OECD Guidelines state that chronic studies should test at least 50 male and 50 female rodents per dose, subchronic studies should test at least 10 male and 10 female rodents per dose, and subacute studies should test at least 5 male and 5 female rodents per dose (OECD, 2018, 2024). Studies with too few animals have low statistical power and may not produce reliable information on chemical carcinogenesis (Percie du Sert *et al*., 2020; OECD, 2018, 2024).

The starting sample size is also necessary to estimate attrition (the number of animals that have been excluded from analysis) and identify in which groups attrition occurred. I concluded that stronger studies accounted for all the animals throughout the experiment, and reported all animals that were excluded from analyses, along with the rationale for their exclusion. A high attrition rate that is not described or accounted for, particularly when the attrition rate differs across treatment groups, can result in unsupported conclusions (Percie du Sert *et al*., 2020).

Chemical Administration and Characterization

I concluded that stronger studies provided comprehensive information about the test substance, including its purity and source, verified the purity of the test substance, and took steps to ensure the accuracy of reported exposure levels or doses. Using a high-purity (*i.e.*, ≥95%) chemical in carcinogenicity studies can help ensure that the observed responses are caused by the chemical itself, rather than contaminants (OECD, 2018, 2024). Chemical stability should also be confirmed (OECD, 2018, 2024).

Exposure Conditions

I considered stronger studies to be those that used a sensitive exposure protocol, including the use of several doses below that associated with early mortality, and an appropriate exposure duration for the outcome of interest. The maximum tolerated dose (MTD), which is the highest dose that does not cause toxicity, can be determined from subchronic studies and then used in chronic study, along with lower doses (half of the MTD and a quarter of the MTD, for example), in case the highest dose selected leads to excessive mortality. This approach also contributes information on dose-response relationships.

Ideally, carcinogenicity bioassays in rats and mice begin at 6 weeks of age and span 104 or 78 weeks, respectively, which includes early adulthood through what would be analogous to a significant part of the occupational lifespan in humans (OECD, 2018, 2024). Longer exposure durations may mask effects due to background tumor incidence, while shorter exposure durations reduce sensitivity in detecting late-appearing tumors related to the chemical exposure (OECD, 2018, 2024).

Outcome Evaluation

The outcome measures in a bioassay include any information recorded to evaluate the chemical's effects. I considered studies to be stronger if they evaluated each outcome of interest using established, standardized methods over an appropriate observation period, *i.e.*, 24 months (104 weeks), representing the majority of the rodent lifespan (OECD, 2018). Histopathology is the primary method for evaluating outcomes in carcinogenicity bioassays. A proper assessment includes a thorough evaluation of all organs and tissues in each animal to detect neoplastic and non-neoplastic lesions. Moribund animals should be removed from the study to prevent tissue autolysis (OECD, 2018, 2024). Autolysis can interfere with the detection of neoplastic and non-neoplastic lesions, reducing the power of the study (NTP, 2006). When mortality rates differ between dose groups, comparisons and tumor trend analyses should be conducted using survival-adjusted tumor rates. Failing to adjust for survival differences could yield unreliable cancer risk estimates and potential misinterpretations of site-specific effects. Studies that sacrificed animals when moribund, or at the end of their natural lifespans, are less reliable than those studies that sacrificed animals at scheduled time points, due to late-life background pathology (OECD, 2018, 2024).

3.3.2.2 Mechanistic Studies

Several mechanisms have been proposed by which TCE, PCE, benzene, and vinyl chloride could cause cancer generally or bladder cancer specifically. I conducted a high-level review of relevant mechanistic evidence to determine whether it supports any biologically plausible mechanism or MoA for cancer with respect to any of these chemicals. I identified relevant mechanistic studies from agency documents (discussed above), recent literature reports, and Plaintiff expert reports (Hatten 2024; Gilbert 2024; Plunkett 2024; Culp 2024; Bird 2024).

I considered the quality of *in vivo* mechanistic studies in a similar manner to the way in which I considered the quality of animal carcinogenicity studies. For *in vitro* studies, I focused on factors that generally have a large impact on the interpretation of the results, including the consistency and reliability of the reported results and the overall relevance of the treatment (*i.e.*, dose, route, and duration) and model system (human, non-human mammalian, non-mammalian) used, with consideration for whether there were any factors that may have biased the results (*e.g.*, differences in culture conditions, high levels of non-specific cytotoxicity, increased cell passages, lack of relevant detoxification pathways, co-exposures, reagent production lots, and infections).

3.3.3 Study Quality and Human Relevance Evaluation

As discussed in Sections 3.3.1 and 3.3.2, I conducted a formal quality assessment of cohort and case-control studies and chronic animal carcinogenicity studies. Because the cutoffs for higher and lower quality are subjective, I did not simply categorize studies as higher or lower quality, but rather reviewed each study with the above quality aspects in mind and determined how each aspect impacted the interpretation of both the individual study's results and the body of literature as a whole.

The quality criteria for animal carcinogenicity studies are focused on internal validity, or the degree to which the results are free from bias and are not due to methodological limitations. I also considered external validity, which is whether an animal study's results have human relevance (Aleksunes and Eaton, 2019). If a study has poor internal validity, then it cannot have external validity. Thus, low-quality animal studies, as determined generally based on exposure conditions and the outcome evaluation, both of which are likely to impact the interpretation of a study's results, have limited human relevance. Also, by design, animal carcinogenicity studies test high doses of chemicals that are generally not directly relevant to human environmental or occupational exposures (Goodman *et al.*, 2020). Regardless, I considered animal carcinogenicity studies to have adequate human relevance if they tested more than one dose; evaluated an inhalation, oral, or dermal route of exposure; and provided relevant data.

Although I did not conduct a formal quality assessment of *in vivo* and *in vitro* mechanistic evidence, I considered the overall biological plausibility and relevance of this evidence to humans, including the dose levels at which the mechanistic event was observed, whether the observed mechanistic event represents an adverse effect, whether this adverse effect is relevant to a cancer pathway, and any fundamental differences between the test systems and humans. I also considered whether events were consistent with and specific for carcinogenesis generally and bladder cancer specifically. For example, changes in gene and protein levels may represent normal biological responses of cells to their environment and are not necessarily associated with adverse effects. In addition, *in vitro* studies typically use experimental systems that lack the normal suite of detoxification pathways (*e.g.*, DNA repair) present in whole organisms and often use high doses that are not relevant to humans. As a result, chemicals can produce false positive results in *in vitro* assays for cancer related mechanisms (*e.g.*, genotoxicity) due to the absence of normal detoxification and repair processes and/or non-specific effects related to the high doses used (US EPA, 2022).

Similarly, with respect to the key characteristics of carcinogens (KCCs) paradigm, which is based on the concept that human carcinogens often demonstrate activity for at least one of 10 key characteristics (*i.e.*., electrophilicity, genotoxicity, alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, induces chronic inflammation, causes immunosuppression, modulates receptor-mediated effects, causes immortalization, and alters cell proliferation, cell death, or nutrient supply), the observed effects from exposure to a given compound may not be evidence of an adverse effect and activity for a given KCC does not necessarily mean that the compound could produce cancer through this activity. For example, increased oxidative stress and can be the result of normal physiological processes and is not specific to carcinogens, as numerous compounds that do not cause cancer have been shown to

cause oxidative stress. Further, not all genotoxicants are carcinogens. Whether a chemical is capable of causing cancer cannot be conclusively determined without carcinogenicity testing in animals. Thus, KCC activity should not be relied upon in isolation to determine whether a chemical poses a carcinogenic risk to humans (Goodman and Lynch, 2017; Goodman *et al*., 2018; Becker *et al*., 2017).

3.4 Evidence Integration

To determine whether an exposure is causally associated with a health outcome, it is critical to integrate the evidence across scientific disciplines. It is only by considering the available evidence, as a whole, that an informed conclusion regarding disease causation can be made. There are a number of methods for evaluating scientific evidence (*e.g.*, Rhomberg *et al*., 2011; Adami *et al*., 2011), all of which emphasize a systematic and transparent approach to the analysis.

Perhaps the most widely used approach for assessing general causation (either as proposed or with slight modifications), including by many regulatory agencies, is that outlined by Sir Austin Bradford Hill in his address to the British Royal Academy of Medicine in 1965 (Hill, 1965; Garabrant, 2000). Dr. Hill put forth several considerations to help address, as he stated, "In what circumstances can we pass from observed association to a verdict of causation? Upon what basis should we proceed to do so?" (Hill, 1965). These considerations are described in Table 3.4, below.

Table 3.4 Bradford Hill Considerations

Aspect	Analysis
Strength of Association	Although a modest risk does not preclude a causal association, I considered an observed risk less likely to be due to chance, bias, or other factors if it was large and precise.
Consistency	Consistency refers to the reproducibility of findings within and across studies. Discordant results may indicate that findings of effect in certain studies are likely due to chance, bias, or confounding factors. If results are consistent only among studies with similar designs, people, places, circumstances, or times, I concluded that this evidence of association is not as strong as consistent results among studies of different designs, or of different people, places, circumstances, and times.
Specificity	Hill (1965) noted that if "the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation." This is true for any type of exposure. I concluded that, as noted by Hill (1965), "if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence."
Temporality	I concluded that a causal interpretation is strengthened when an exposure is known to precede the occurrence of a disease. Temporality is the least definitive (but 100% necessary) of the Bradford Hill considerations, because many events occur prior to the development of a disease that may have nothing to do with its cause.
Dose-Response	To determine whether a dose-response relationship exists, I compared risks across exposure groups and related exposure to dose. I did this using risk estimates based on internal comparisons (*e.g.*, RRs or ORs) or risk estimates based on populations with similar age distributions.

Aspect	Analysis
Biological Plausibility	I concluded that if the available evidence indicates there is a biological mechanism for an adverse effect to occur under relevant exposure conditions, and this is sufficient to allow a scientifically defensible determination for causation in humans, this can add weight to an association reported in epidemiology studies. For example, if a chemical causes cancer in animal models, then it may be biologically plausible that it can also cause cancer in humans. Similarly, data regarding specific MoAs may also provide evidence that carcinogenicity in humans is biologically plausible, particularly in a particular organ. Conversely, if the evidence indicates that a biological mechanism is not plausible in humans, that places doubt on the epidemiology findings.
Coherence	To address coherence, I evaluated whether all of the known facts related to a chemical exposure and bladder cancer, particularly with respect to epidemiology, animal carcinogenicity, and MoA evidence, fit together in a consistent manner.
Experiment	If a substance is a causal factor in a disease process, then the association between an exposure and an effect should be altered by an experiment of preventative action. However, it is often not possible or practical to conduct such experiments. If such experiments have been conducted, I concluded causality was more likely if preventive action altered associations.
Analogy	The final consideration is often difficult to meet. I concluded that if there is evidence for a similar effect after exposure to a similar agent, this also adds support for a causal association.

Notes:
MoA = Mode of Action; OR = Odds Ratio; RR = Relative Risk.

These considerations have been interpreted in various ways since they were first promulgated in the 1960s. With respect to strength of association, there is no specific cutoff for a strong association that has been generally accepted. US EPA (2019) characterized risk estimates between 1 and 1.3 as indicting a slight positive association, from 1.3 to <2 as indicating a positive association, from 2 to <3 as indicating a moderately strong association, and >3 as indicating a strong association. I am not aware of any framework that suggests a risk estimate of 1.1 indicates a strong association, except for ATSDR (2017a), as discussed in Section 3.5.2. In contrast, it is possible that a risk estimate >3 in an environmental epidemiology study, particularly if it has wide CIs, quite likely resulted from chance due to a small number of exposed cases. Because of this, only if the preponderance of high-quality epidemiology studies reports associations that cannot be explained by non-causal alternatives (*i.e.*, only if results are consistent), is a causal association supported. If studies are of low quality or if results are generally not consistent across studies, then it is more likely that positive associations are a result of chance, bias, or confounding.

This is also true for dose-response. Only consistent evidence of similar dose-response relationships in high-quality epidemiology studies supports causation. That is, if some studies suggest monotonic dose-response, and others support non-monotonic dose response, this is not consistent evidence of a dose-response relationship. If dose-response relationships are not found consistently across high-quality studies, this suggests non-causal explanations are more likely.

Dr. Bradford Hill noted that there might be occasions when information on biological plausibility is not available (Hill, 1965). If data are available, however, they should not be ignored or, conversely, overinterpreted. In some cases, there may be evidence to demonstrate that a carcinogenic MoA is not plausible. In other cases, if there is evidence that an agent can cause an effect on an organism, but there is no evidence that the magnitude of the effect is sufficient to lead to cancer, or if the effect is something common to carcinogens and noncarcinogens, this should not be considered evidence of biological plausibility. This concept should also be considered when evaluating coherence.

Keeping these caveats in mind, I note that the Bradford Hill considerations are not intended as a checklist from which causality can be concluded, but rather allow for drawing informed conclusions based on

available evidence. Overall, I relied on these considerations to determine whether an association is likely to be causal or whether other explanations are more likely (Ward, 2009). As stated by Dr. Hill (1965):

> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as *sine qua non.* What they can do, with greater or less strength, is to help us make up our minds on the fundamental question – is there any other way of explaining the facts before us, is there any other answer equally, or more, likely than cause and effect?

In summary, I evaluated study quality to determine how reliable the results of individual studies were for addressing causation, and then considered individual study results in the context of study quality. I then integrated epidemiology, toxicology, and MoA evidence, with a particular focus on higher-quality studies, in the context of the Bradford Hill considerations for TCE, PCE, benzene, and vinyl chloride in Sections 6.3, 7.3, 8.3, and 9.3, respectively, to evaluate whether the evidence as a whole supports causality. Too few studies were available to conduct this type of assessment for *trans*-1,2-DCE.

3.5 Agency Reviews

3.5.1 Overview

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct evaluations of chemical carcinogenicity. IARC, US EPA, and NTP all classify chemicals according to how likely it is that they are human carcinogens, each using a unique framework, as shown in Table 3.5. NASEM and ATSDR do not classify agents according to their human carcinogenicity potential (an exception being ATSDR [2017a], as discussed below). NASEM, ATSDR, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Table 3.6.

Table 3.5 Agency Cancer Classification Frameworks

Agency/ Source	Classification	Description[a]
IARC (2019)	Group 1 (carcinogenic to humans)	[A]pplies whenever there is *sufficient evidence of carcinogenicity* in humans. In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.
	Group 2A (probably carcinogenic to humans)	[G]enerally applies when the Working Group has made at least *two of the following* evaluations, *including at least one* that involves either exposed humans or human cells or tissues: ▪ *Limited evidence of carcinogenicity* in humans, ▪ *Sufficient evidence of carcinogenicity* in experimental animals, ▪ *Strong evidence that the agent exhibits key characteristics of carcinogens.* If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems.
	Group 2B (possibly carcinogenic to humans)	[G]enerally applies when only one of the following evaluations has been made by the Working Group: ▪ *Limited evidence of carcinogenicity* in humans, ▪ *Sufficient evidence of carcinogenicity* in experimental animals, ▪ *Strong evidence that the agent exhibits key characteristics of carcinogens.*
	Group 3 (not classifiable as to its carcinogenicity to humans)	Agents that do not fall into any other group are generally placed in this category. This includes when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of *sufficient evidence in experimental animals*, and other categories are not supported by data from studies in humans and mechanistic studies. An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.
IARC (2018)	Group 4 (probably not carcinogenic to humans) [Eliminated in 2019]	This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Agency/ Source	Classification	Description[a]
US EPA IRIS (US EPA, 1986)	Group A (carcinogenic to humans)	[T]here is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.
	Group B (probably carcinogenic to humans)	[T]he weight of evidence of human carcinogenicity based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups.... Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies.... Agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under Group B2.
	Group C (possibly carcinogenic to humans)	[L]imited evidence of carcinogenicity in animals in the absence of human data.
	Group D (not classifiable as to human carcinogenicity)	[A]gents with inadequate human and animal evidence of carcinogenicity or for which no data are available.
	Group E (evidence of non-carcinogenicity for humans)	[N]o evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.
US EPA (2005)[a]	Carcinogenic to humans	[C]onvincing epidemiologic evidence of a causal association between human exposure and cancer.... It can be used when all of the following conditions are met: (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, and (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information.
	Likely to be carcinogenic to humans	[T]he weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans."
	Suggestive evidence of carcinogenic potential	[T]he weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species.
	Inadequate information to assess carcinogenic potential	[A]vailable data are judged inadequate for applying one of the other descriptors. Additional studies generally would be expected to provide further insights.

Agency/ Source	Classification	Description[a]
	Not likely to be carcinogenic to humans	[T]he available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic.
NTP (2023)	Known to be a human carcinogen	There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.
	Reasonably anticipated to be a human carcinogen	There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR [T]here is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors(1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, type of tumor, or age at onset, OR [T]here is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Notes:
IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NTP = National Toxicology Program; US EPA = United States Environmental Protection Agency.
(a) Description text taken directly from the cited sources. All emphasis is in the original source.

Table 3.6 IARC Classification Framework for Evaluating the Strength of Human, Experimental Animal, and Mechanistic Evidence of Cancer (IARC, 2019)

Realm	Classification	Description[a]
Cancer in Humans	Sufficient evidence of carcinogenicity	A causal association between exposure to the agent and human cancer has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.
	Limited evidence of carcinogenicity	A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.
	Inadequate evidence of carcinogenicity	The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Realm	Classification	Description[a]
	Evidence suggesting lack of carcinogenicity	There are several high-quality studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and the studied cancers at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit below or close to the null value (*e.g.* a relative risk of unity). Bias and confounding were ruled out with reasonable confidence, and the studies were considered informative. Evidence is limited to the cancer sites, populations and life stages, conditions and levels of exposure, and length of observation covered by the available studies.
Cancer in Experimental Animals	Sufficient evidence of carcinogenicity	A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols. An increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in both sexes of a single species in a well-conducted study, ideally IARC Monographs Preamble conducted under Good Laboratory Practices (GLP), can also provide sufficient evidence. A single study in one species and sex may be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour, or age at onset, or when there are marked findings of tumours at multiple sites.
	Limited evidence of carcinogenicity	The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment and does not meet the criteria for sufficient evidence; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation-promotion studies; (e) the evidence of carcinogenicity is restricted to observational studies in non laboratory animals (*e.g.* companion animals); or (f) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.
	Inadequate evidence of carcinogenicity	The studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data are available on cancer in experimental animals.
	Evidence suggesting lack of carcinogenicity	Well-conducted studies (*e.g.* conducted under GLP) involving both sexes of at least two species are available showing that, within the limits of the tests used, the agent was not carcinogenic. The conclusion of evidence suggesting lack of carcinogenicity is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure covered by the available studies.

Realm	Classification	Description[a]
Mechanistic Evidence	Strong evidence	Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species. Quantitative structure-activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence.
	Limited evidence	The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.
	Inadequate evidence	Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of IARC Monographs Preamble the design, conduct, or interpretation of the studies; (c) the available result are negative.

Note:
IARC = International Agency for Research on Cancer.
(a) Description text taken directly from IARC (2019).

The methods by which these agencies conduct their reviews vary, though all strive to use an objective systematic approach to review the scientific literature. These reviews generally involve many researchers and peer-reviewers and take years to complete. For example, ATSDR generates Toxicological Profiles, which reflect "a comprehensive and extensive evaluation, summary, and interpretation of available toxicological and epidemiological information on a substance" (ATSDR, 2024a).

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, these reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. This is sometimes a result of the frameworks themselves. For example, IARC (2019) concludes that an agent is a possible carcinogen (Group 2B) if there is "limited evidence of carcinogenicity in humans," "sufficient evidence of carcinogenicity in experimental animals," *or* "strong evidence that the agent exhibits key characteristics of carcinogens."

Limited evidence in humans means that "chance, bias, or confounding could not be ruled out with reasonable confidence" (IARC, 2019). If this is the case, one should not conclude the agent is a possible carcinogen, but that the data are not sufficient to make a scientifically informed judgment. This is consistent with the IOM (2009) hierarchy, which states that "if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above."

Similarly, as noted above, the 10 KCCs on their own are not informative with respect to cancer risk, as many chemicals that are not carcinogenic share these characteristics (Goodman and Lynch, 2017; Goodman *et al.*, 2018; Becker *et al.*, 2017).

The US EPA and NTP carcinogenicity categories include ones similar to IARC's Group 2B ("possibly carcinogenic to humans"): "possibly carcinogenic to humans" and "reasonably anticipated to be a human carcinogen," respectively (US EPA, 2005; NTP, 2023). As with agents categorized in IARC's Group 2B, the available evidence for agents placed into the equivalent US EPA and NTP categories is generally not sufficient to make a scientifically informed judgment regarding their ability to cause cancer in humans. As such, for agents in IARC's Group 2B, US EPA's "possibly carcinogenic to humans" category, and NTP's "reasonably anticipated to be a human carcinogen" category, it is **not** always the case that the scientific evidence demonstrates that the agents are at least as likely as not to be human carcinogens. Rather, these classification categories indicate that additional evidence is required to make a scientifically informed conclusion regarding the carcinogenicity of the agent.

Regardless of the classification, it is important to note that classifications for all agents are based on specific cancer types. When an agency classifies a chemical as to its likelihood of being carcinogenic to humans, this classification does not apply to all cancer types.

3.5.2 ATSDR (2017a) Assessment

The review process for the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) was quite different than those discussed above. ATSDR (2017a) stated, "The purpose [of this report] was to assess the strength of the evidence supporting causality of adverse health effects from exposures to the drinking water contaminants at Camp Lejeune. This report represents ATSDR's assessment of the state of evidence at this time." This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation. Its conclusions regarding causation for many health outcomes are inconsistent with those of several other agency reviews, including those by ATSDR.

3.5.2.1 Resources

In his recent deposition, Dr. Bove (2024a) indicated that he was the sole author of this report. He noted that a few senators requested that he conduct this review over a 6-week period. He stated, "During that period, I had enough material together so that it was peer-reviewed by two people to give their advice. One person liked it, one person didn't like it, but that – so – and I took their comments into account. And we briefed the VA researchers/scientists… And for the most part, they agreed with what my – with what my assessment was. There were some disagreements."

It is simply not possible to conduct an objective, systematic review of four chemicals with a considerable amount of data and 16 health outcomes in 6 weeks. Systematic reviews can take months or years for teams of researchers to complete, and they then generally undergo a rigorous peer-review process. Bove (2024a) even acknowledged that this type of review was unusual to conduct at ATSDR.

3.5.2.2 Statistical Significance

With respect to evaluating individual studies, ATSDR (2017a) did not "use significance testing to assess the evidence for causality." ATSDR (2017a) stated, "There are several limitations to the use of statistical significance testing (Rothman *et al.* 2008, Goodman 2008, Stang *et al* 2010). Moreover, a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association, while a finding that achieves statistical significance can often lack scientific and public health significance." ATSDR (2017a) instead relied heavily on a concept later defined by Bove *et al*. (2024a,b) as a Confidence

Interval Ratio (CIR). This is the ratio of the upper 95% confidence limit to the lower 95% confidence limit. This is not a generally accepted metric in the field of epidemiology.

The report states that in a high-quality epidemiology study, "the effect of biases on the study's findings was probably low and the precision of the effect estimate was adequate, *e.g.*, the width of the 95% confidence interval as measured by the ratio of the upper to lower limit is ≤ 3." Elsewhere the report states that "an effect estimate (*e.g.*, risk ratio, odds ratio, or standardized mortality ratio) was considered to have good precision (or less uncertainty) if the ratio of the upper limit to lower limit of its 95% confidence interval was ≤ 2." It is not clear what the basis of these cutoffs were or why they were not the same.

While it is true that statistical significance should not be the only consideration for whether an association is causal, it is not appropriate to simply ignore it. As noted in Section 3.1.1, a 95% CI is derived to indicate a range of the sample risk ratio that has a 95% probability of capturing the true population risk ratio. If a sample risk ratio's 95% CI does not contain 1, there is a 95% probability that the underlying population's risk ratio is different from 1, indicating that we can reasonably exclude chance as an explanation (Naimi and Whitcomb, 2020). In contrast, if a sample risk ratio's 95% CI contains 1, one cannot confidently exclude the possibility that the underlying population's risk ratio is 1 (*i.e.*, there is no association). In other words, the sample risk ratio on its own does not provide statistically meaningful evidence for the existence of an association in the population.

In some cases, a true association in a population will not be statistically significant (*e.g.*, the 95% CI includes 1 or the p-value is ≥0.05) because the sample is too small to detect it or other factors are masking the association (*e.g.*, exposure misclassification). For this reason, one cannot conclude with certainty that there is no association if a result is not statistically significant, only that the study does not provide evidence that there is an association. Conversely, a statistically significant result may not reflect a true or clinically relevant difference at the population level. However, if one were simply to ignore statistical significance, every single association studied would either support causation or a protective effect; there would be few true null results. I also note that the CIR is completely dependent on significance testing, only with less stringent criteria for what is considered "significant." That is, it appears to be a work-around for when statistical significance is not achieved, even though it is based on the same statistics.

Flaws with this reasoning are evident in the number of health conditions that ATSDR (2017a) concluded are causally associated with volatile organic compound (VOC) exposure. Every chemical has some degree of specificity with respect to the health conditions it can cause, and it defies logic that the chemicals discussed in this report can cause many health conditions known to have very different MoAs.

3.5.2.3 Study Quality

ATSDR (2017a) discussed several limitations of the studies it evaluated but appears to downplay the impact of these limitations on the interpretation of these studies' results. For example, the report stated, "Drinking water studies included in this review based their exposure assessments on modeled historical estimates of contaminant levels in the drinking water serving residences or workplaces. Information on the amount of water consumed by individuals was either limited (due to likely inaccuracies in the recall of past consumption habits) or unavailable." This can result in major exposure misclassification, but that is not adequately considered in this report.

Similarly, ATSDR (2017a) discussed confounding, but tends to downplay its impact, for example, indicating that "substantial confounding due to smoking or any other risk factor is rare in occupational and environmental epidemiology." However, smoking is a major confounder for several cancers. Even if

smoking or another factor is not a confounder *per se*, but is associated with a health outcome, it should be considered in a rigorous manner.

In addition to these issues, ATSDR (2017a) did not review studies in a systematic manner. It is not clear how studies were selected to be discussed. Study quality is not evaluated in a systematic manner, and sometimes is not discussed at all.

3.5.2.4 Strength of Evidence

Perhaps most importantly, the criteria used in the ATSDR (2017a) report are not appropriate. ATSDR (2017a) claimed that it based its criteria on those put forth by the Institute of Medicine (IOM) in its report, "Improving the Presumptive Disability Decision-Making Process for Veterans" (IOM, 2008). The requirements for categorizing levels of evidence for causation by IOM (2008) and ATSDR (2017a) are shown in Table 3.7. For each category, IOM (2008) requires more scientific evidence than ATSDR (2017a) does. For example, for the causal category, ATSDR (2017a) indicated that consistent positive associations >1.1 provide evidence for causation. The report does not discuss whether study quality needs to be considered when determining causality – only study utility (though utility is not defined in the report). In addition, ATSDR (2017a) does not cite a source for the cutoff of 1.1. A risk estimate of 1.1 is generally considered quite weak, and even a small amount of bias or confounding could influence a risk estimate by 10%. For example, in a recent review, US EPA (2019) characterized risk estimates from epidemiology studies as follows:

- no evidence of a positive association between exposure and outcome (*e.g.*, OR = 1.00; OR < 1.00);
- no evidence of a significant positive association (*e.g.*, OR > 1.00 but not significant);
- evidence of a slight positive association (*e.g.*, 1.00 < OR < 1.30 and significant);
- evidence of a positive association (*e.g.*, 1.30 ≤ OR < 2.0 and significant); and
- evidence of a moderately strong (*e.g.*, 2.0 ≤ OR < 3.0 and significant) or strong *(e.g.*, OR ≥ 3.0 and significant) positive association.

The criteria listed by ATSDR (2017a) for classifying evidence as equipoise and above are more consistent with the IOM (2008) criteria for *below equipoise* in that only one "high utility" epidemiology study with a risk estimate of 1.1 or above is required. What constitutes a "high utility" study is not clearly defined, and there is no indication that results of this one required study must be consistent with other studies, or that this risk estimate even needs to be statistically significant. ATSDR (2017a) also considers evidence above equipoise if "[t]he degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality." There is no requirement that these experimental studies be high quality or relevant to humans. ATSDR (2017a) does not provide any criteria for evidence against causation.

It is notable that several other agency reviews include an analysis of the level of evidence for causation for the health conditions evaluated by ATSDR (2017a). While some of these reviews reach similar conclusions for certain health outcomes (*e.g.*, benzene and leukemia/acute myeloid leukemia [AML]), as a whole, ATSDR (2017a) tends to conclude the evidence is stronger than other agency reviews do, including other reviews by ATSDR. For example, most government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020c), or did not draw any conclusions regarding this potential association (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015). In contrast, ATSDR (2017a) concluded that the evidence for TCE and leukemia was "sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists."

I provide brief summaries of bladder cancer assessments in agency reviews of TCE, PCE, benzene, and vinyl chloride in Sections 6.4, 7.4, 8.4, and 9.4, respectively.

Table 3.7 IOM (2008) and ATSDR (2017a) Hierarchies of Evidence for Causation[a]

Level of Evidence	IOM (2008)	ATSDR (2017a)
Sufficient	If the overall evidence for a causal relationship is categorized as Sufficient, then it should be scientifically compelling. It might include ▪ replicated and consistent evidence of a causal association: that is, evidence of an association from several high-quality epidemiologic studies that cannot be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding), or ▪ evidence of causation from animal studies and mechanistic knowledge, or ▪ compelling evidence from animal studies and strong mechanistic evidence from studies in exposed humans, consistent with (*i.e.*, not contradicted by) the epidemiologic evidence.	[T]he evidence is sufficient to conclude that a causal relationship exists. This category would be met, for example, if: 1. There is sufficient evidence from human studies in which chance and biases (including confounding) can be ruled out with reasonable confidence, or 2. There is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a relevant mechanism in humans. Sufficient evidence from human studies can be provided by a meta-analysis and/or by several studies considered to have high utility. Considerations in assessing the evidence include several of Hills viewpoints: (1) temporal relationship, (2) consistent positive associations (*e.g.*, risk ratio or odds ratio greater than 1.1), (3) magnitude of the effect estimate (*e.g.*, risk ratio, odds ratio), (4) exposure-response relationship, and (5) biological plausibility (Hill 1965).

Level of Evidence	IOM (2008)	ATSDR (2017a)
Equipoise and above	To be categorized as Equipoise and Above, the scientific community should categorize the overall evidence as making it more confident in the existence of a causal relationship than in the non-existence of a causal relationship, but not sufficient to conclude causation. For example, if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above. Alternatively, if there is strong evidence from animal studies or mechanistic evidence, not contradicted by human or other evidence, then the overall evidence might be categorized as Equipoise and Above.	The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if: 1. The degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality, or 2. A meta-analysis does not provide convincing evidence (*e.g.*, the summary risk estimate is close to the null value of 1.0, *i.e.*, ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence. 3. A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

Level of Evidence	IOM (2008)	ATSDR (2017a)
Below Equipoise	To be categorized as Below Equipoise, the overall evidence for a causal relationship should either be judged not to make causation at least as likely as not, or not sufficient to make a scientifically informed judgment. This might occur 1. when the human evidence is consistent in showing an association, but the evidence is limited by the inability to rule out chance, bias, or confounding with confidence, and animal or mechanistic evidence is weak, or 2. when animal evidence suggests a causal relationship, but human and mechanistic evidence is weak or inconsistent, or 3. when mechanistic evidence is suggestive but animal and human evidence is weak or inconsistent, or 4. when the evidence base is very thin.	The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment. This is a rather broad category that encompasses: ▪ evidence sufficient to conclude an association exists but where there is some doubt that biases can be ruled out and the animal and mechanistic evidence is weak, or ▪ evidence for an association that is so limited that there is substantial doubt that biases can be ruled out, or ▪ insufficient evidence to determine whether an association exists.
Against	To be categorized as Against, the overall evidence should favor belief that there is no causal relationship from exposure to disease. For example, if there is human evidence from multiple studies covering the full range of exposures encountered by humans that are consistent in showing no causal association, or there is animal or mechanistic evidence supporting the lack of a causal relationship… then the scientific community should categorize the evidence as Against causation	The evidence suggests the lack of a causal relationship.

Note:
(a) Description text taken directly from IOM (2008) and ATSDR (2017a), respectively.

4 Carcinogenicity

4.1 Overview

Cancer is a term used to describe a group of over 100 chronic diseases that can develop in almost every part of the body (ACS, 2019a). Because organs and tissues are made up of several types of cells, several different types of cancer can arise in the same organ or tissue (ACS, 2019a). The "defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, which can then invade adjoining parts of the body and spread to other organs" (WHO, 2018). Chemical carcinogens impact specific biological pathways and each can only cause specific cancer types (ACS, 2019b; Meek *et al*., 2014; US EPA, 2005). For example, benzidine causes only bladder cancer in humans (IARC, 2012a). Also, the cancer types caused by carcinogens can vary across humans and animals, and some chemicals that can cause cancer in some species do not cause cancer in others (US EPA, 2005).

Carcinogenic substances can only affect cells by specific MoAs. The MoAs of known or suspected carcinogens are investigated based on physical, chemical, and biological information that explains key events in the development of cancers. While some carcinogens may have more than one MoA, as indicated by Meek *et al*. (2014), "In general, mode of action analysis applies to a single effect in a single tissue. In essence, there is one mode of action leading to an effect of interest in the relevant organ for a given substance." Carcinogens can only affect tissues that they, or their metabolites, can physically access. A carcinogenic substance cannot cause cancers in tissues that it cannot reach (US EPA, 2005).

If a substance can cause cancer, this can only occur with sufficient exposure (Wolf *et al*., 2019). For example, high doses of ionizing radiation can cause cancer, but low doses cannot (ATSDR, 1999; Dobrzynski *et al*., 2015; HPS, 2020).

One of the primary characteristics of cancer is the latency period. According to the National Research Council (NRC, 2001):

> For cancers, there is generally a period of time, which may be as long as several decades, between a critical molecular interaction of a carcinogen within a single cell and the first appearance of a malignant cell. The length of this period will vary based on the nature of the cancer and whether the molecular interaction occurs early or late in the chain of events leading to the cancer. That period between the critical exposure to the carcinogenic agent and the occurrence of the cancer is referred to as the latency period. Latency is usually estimated by determining the period between the time of first exposure to the carcinogen and the clinical detection of the cancer.

Latency periods are disease specific and, for cancer, can range from <1 year (*e.g*., leukemias following low-level ionizing radiation [CDC, 2015]) to several decades (*e.g*., lung cancer development from smoking [CDC, 2014; Weisenburger, 1992; Weiss, 1997; Smith, 2001; Bilello *et al*., 2002; US PHS, 2004]). If a chemical exposure can cause cancer, it is often necessary for the exposure to occur repeatedly over a long period of time that is sufficiently before disease onset (*i.e*., at the beginning of the latency period).

In some cases, there is evidence that a chemical can only cause cancer within a certain time frame. For example, evidence suggests that benzene most likely only causes cancer within 10 to 15 years of exposure (Rhomberg *et al*., 2016).

It is often not known what the cause of cancer in a specific individual is or why one person develops cancer while another does not (NCI, 2015). While some researchers have suggested that extrinsic risk factors may play a large role in cancer causation (*e.g*., McGuinn *et al*., 2012; Whiteman and Wilson, 2016; Wu *et al*., 2016), others conclude that the majority of cancers are due to random mutations in deoxyribonucleic acid (DNA) that can arise during normal cell division (Tomasetti and Vogelstein, 2015). In these cases, mutations arise normally as errors in cell division and are not associated with specific chemicals or physical agents (meaning they occur naturally, not as a result of an exogenous exposure). Most of these mutations are repaired by the body, but some escape normal repair mechanisms, in some cases due to immune system irregularities (Johns Hopkins Medicine, 2019).

According to the American Cancer Society (ACS), "having a risk factor, or even several, does not mean that you will get the disease. Many people with one or more risk factors never get cancer, while others who get cancer may have had few or no known risk factors" (ACS, 2019c). Increasing age is considered the most important cancer risk factor, though cancer may develop at any age (NCI, 2015). Genetic changes that cause cancer can be inherited; therefore, a family history of cancer can indicate that a person may be genetically predisposed to develop cancer (NCI, 2017). There are also common, modifiable lifestyle factors that contribute to the development of cancer. For example, people who smoke or who are exposed to secondhand smoke have an increased risk of cancer. In fact, Johns Hopkins Medicine states that "cancerous tumors from the use of tobacco are the leading cause of deaths from cancer" (Johns Hopkins Medicine, 2019). In addition to smoking, being overweight or obese increases a person's risk of developing certain types of cancer (NCI, 2015). Other common risk factors for cancer include radiation and extreme sun exposure (Johns Hopkins Medicine, 2019).

4.2 Bladder Cancer

Urothelial or transitional cell carcinoma (TCC), which is the most common type of bladder cancer, forms in the urothelial cells that line the inside of the bladder or the upper urinary tract (*i.e*., renal pelvis and ureter). The majority of TCC cases involve the bladder, while upper tract urothelial carcinoma (UTUC) is relatively rare, accounting for only approximately 5-10% of TCCs and only 5-10% of all kidney cancers (Green *et al*., 2013; ACS, 2020). Differences in tissue embryology and morphology, genetics, gender susceptibility, prognosis, and disease management suggest that that UTUC and TTC of the bladder should be considered distinct diseases even though both originate from urothelial cells (Green *et al*., 2013; Leow *et al*., 2017). Despite these differences, most toxicity and epidemiology studies do not differentiate between TCC of the bladder and upper urinary tract. Therefore, for the purpose of my assessment, all urothelial cell cancers are considered with bladder cancer, unless specifically stated that they occur in the upper tract. Other types of bladder cancer and the proportion of bladder cancer cases they make up include squamous cell carcinoma (1-2%), adenocarcinoma (~1%), small cell carcinoma (<1%), and sarcoma (very rare) (ACS, 2016).

NCI estimated that, in 2024 in the US, there would be 81,190 new cases and 16,840 deaths due to bladder cancer. Bladder cancer is expected to represent approximately 4.2% of all new cancer cases in 2024 in the United States (US) and, in 2021, there were an estimated 730,044 people in the US living with bladder cancer. NCI reported an overall lifetime risk of being diagnosed with bladder cancer of 2.3% for people in the US, based on data from 2017-2021. Bladder cancer is more common in men than women. From 2017-2021, the overall age-adjusted incidence rate was 31.6 per 100,000 men and 7.8 per 100,000 women in the

US. About 49.6% of all new US bladder cancer cases are diagnosed in people between the ages of 55 and 74 years, with a median age at diagnosis of 73 years (NCI, 2024b).

Bladder cancer has several risk factors, including genetic and lifestyle factors. According to ACS (2024), "Smoking is the most important risk factor for bladder cancer. People who smoke are at least 3 times as likely to get bladder cancer as people who don't. Smoking causes about half of all bladder cancers." Among demographic risk factors, being male, older, and white make it more likely that an individual will develop bladder cancer (ACS, 2024). Other risk factors include prior cancer treatment, chronic bladder inflammation, a personal or family history of bladder cancer, and genetics (Mayo Clinic, 2017; ACS, 2024). There is some evidence that certain medications or dietary factors may be associated with bladder cancer, including the diabetes drug pioglitazone, aristolochic acid-containing supplements, and arsenic in drinking water, while fluid intake is inversely associated with bladder cancer (ACS, 2024).

5 Camp Lejeune Studies

NRC (2009) produced the report, "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects." The report concluded, "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." NRC (2009) went on to say:

> 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.

Despite this, several Camp Lejeune epidemiology studies were conducted after the NRC (2009) report. Below I review five cohort studies that evaluated bladder cancer risks in US Marines and Navy personnel or civilian employees at Camp Lejeune. The characteristics, results, and quality of these studies are detailed in Attachments B and C. Below, I provide brief summaries of the studies and describe important quality considerations that impact the interpretation of study results, followed by a discussion of the study results.

5.1 Study Overview

5.1.1 Study Populations

The study populations examined in the five Camp Lejeune studies overlap but are not identical. All of the studies used appropriate comparison groups. The three mortality studies (Bove *et al*., 2014a,b, 2024a) had high retention and low loss to follow up, largely because of their reliance on historical records for enrollment and outcome ascertainment.

The two studies that reported on incidence (ATSDR, 2018a; Bove *et al*., 2024b) had a higher potential for selection bias. Bove *et al*. (2024b) did not report on retention or loss to follow-up. The cohort study conducted by ATSDR (2018b) reported low response rates to the health survey among military personnel and civilian employees at Camp Lejeune and Camp Pendleton (31% overall). It is not known how those who did not participate differed from those who did.

The compilation of the study cohorts in the four Bove *et al*. (2014a,b, 2024a,b) studies relied on historical records, which likely did not result in any selection bias. ATSDR (2018a) actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018a) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those

> at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

This is supported by the fact that civilian employees at Camp Lejeune had a higher participation rate than civilian employees at Camp Pendleton and Marines at either base (see Table 1 of ATSDR, 2018b).

5.1.2 Exposure Assessment

All five studies included at least some comparisons of bladder cancer risks in Camp Lejeune populations to risks in Camp Pendleton populations without consideration of chemical specific exposures or doses. Three of the studies (Bove *et al*., 2014a, 2024a,b) relied on being stationed or employed at Camp Lejeune as the basis of exposure. Using this broad definition of exposure does not account for actual individual level exposures and fails to consider differences between individuals that could impact their exposure potential (*e.g*., water consumption/exposure). Bove *et al*. (2024a,b) considered disease risk by duration of assignment or employment on base, which is better than only considering whether an individual was ever on base as Bove *et al*. (2014a) did, but it still does not account for chemical concentrations in the water to which each individual was exposed during their assignment or employment and does not link chemical concentrations in drinking water to data on individual water consumption/exposure.

Some studies conducted analyses of Marines and Navy personnel who began active duty before 1975. There are no data available on military unit codes for Marines and Navy personnel who began active duty prior to 1975. These individuals could have been stationed at Camp Pendleton, Camp Lejeune, or elsewhere prior to 1975, leading to exposure misclassification.

Bove *et al*. (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune based on modeled average monthly levels of chemicals in drinking water on base. These levels were estimated based on ATSDR (2007b, 2013) groundwater fate and transport models and data on historical occupation codes, workplace or residence, and period and duration of employment or residence.

Modeled exposure estimates are generally less reliable than direct measurements, particularly when modeled estimates are only based on limited or sparse quantitative information or are not based on any quantitative information. Also, modeled exposure estimates based on chemical concentrations in the groundwater supplying different locations on base depend on the accuracy of the model's assumptions, and, while the time-varying nature of the water concentrations of chemicals were considered in the ATSDR model, the modeled estimates are constrained by the limited timing and frequency of measurements and do not necessarily reflect long-term or even average concentrations.

Drs. Hennet's and Spiliotopoulos's reports show that, for several reasons, including the lack of chemical concentration data prior to 1980 and the lack of reliable data on the start and quantity of contaminant source releases, ATSDR's modeled exposure estimates are biased high, raising questions about quantitative exposure estimates derived from this model (Hennet, 2024; Spiliotopoulos, 2024). Furthermore, without a direct link between measurements or modeled exposure estimates and individual-level water consumption/exposure data, exposure estimates are likely to be even less accurate with respect to individual exposures. Similarly, the ATSDR (2017b) "Public Health Assessment for Camp Lejeune Drinking Water" stated:

> Limitations related to VOCs include the lack of water sampling data prior to 1982, uncertainty about when contamination first occurred in water supplies, reliance on the testing of finished water for leaving the treatment plant rather than at the point of exposure

> (*i.e.* the faucet or shower) for estimating exposure, limited information about site-specific exposure parameters, lack of indoor air samples, uncertainties that are intrinsic to the use of models to predict inputs to the assessment, uncertainties about the combined effects of exposure to the specific mixture of chemicals in the water systems, limitations in the available toxicological data to predict the health impacts of exposure, and lack of specific health outcome data, specifically incidence data for cancer and cardiac defects to confirm the potential effects that are described in this assessment.

Finally, Bove *et al*. (2014b) and ATSDR (2018a) reported near perfect correlations between the TCE, benzene, vinyl chloride, and total VOC categorical exposure variables among Marines and Navy personnel. For civilian employees, ATSDR (2018a) reported that categorical exposure variables for TCE and PCE were nearly perfectly correlated. Therefore, results from these studies are not specific to individual chemical exposures.

With respect to exposure misclassification, ATSDR (2018a) stated:

> Additionally, the study results could have been impacted by exposure misclassification bias. Exposure misclassification bias could have resulted because of errors in base assignments, limited information on each unit's barrack location, lack of information on how much drinking water was consumed at the Marine's residence, lack of data on where a Marine at Camp Lejeune trained on-base and drinking water use during training, inability to accurately capture time spent away from the base for training or deployment, uncertainty about the drinking water use of civilian workers at Camp Lejeune, and uncertainty about workplace locations (*e.g.,* during the workday, a worker might have been assigned to multiple locations at the base). The exposure misclassification bias is likely non-differential because the errors in exposure assignments should be unrelated to diseases status.

Nondifferential exposure measurement error can, but does not always, bias results towards the null (*i.e*., towards a lack of effect). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al*., 1991) or multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in Bove *et al*. (2014b) and ATSDR (2018a), non-differential misclassification can result in bias either toward or away from the null.

5.1.3 Outcome Assessment

Bove *et al*. (2014a, b) and Bove *et al*. (2024a) evaluated cancer deaths among Marines and Navy personnel who were stationed at Camp Lejeune between 1975 and 1985 and civilian workers at Camp Lejeune who were employed full-time between 1972 or 1973 and 1985. Both ATSDR (2018a) and Bove *et al*. (2024b) evaluated cancer incidence among Marines and Navy personnel stationed at Camp Lejeune between 1975 and 1985 and among civilians employed at Camp Lejeune between 1972 and 1985.

All four Bove studies (Bove *et al*. 2014a,b, 2024a,b) used reliable sources to identify cases or deaths (*i.e*., SSA, National Death Index, cancer registries). ATSDR (2018a) confirmed cases using medical records or death certificates, but initially relied on self-reporting to identify cases, which could have resulted in some missed cases. All of the studies had sufficient follow-up time for cancer to develop (range: 22-40 years) but, because bladder cancer is not always fatal, analyses evaluating incidence are more informative than those evaluating mortality. Bove *et al*. (2024b) evaluated bladder cancer risk by subtype: papillary

transitional cell carcinoma (PTCC), non-papillary transitional cell carcinoma (NPTCC), and urothelial, malignant, and *in situ* cancer.

5.1.4 Covariates

ATSDR (2018a) controlled for age, or age and sex, in analyses of Marines and Navy personnel and either did not include any covariates or only controlled for age in analyses of civilian employees. All four Bove studies (2014a,b; Bove *et al*., 2024a,b) controlled for age, sex, and race. Bove *et al*. (2014a, 2024a,b) also controlled for occupation (blue *vs.* white collar) as a proxy for other chemical exposures when evaluating risk among civilian employees. No Camp Lejeune study controlled for other important covariates, including smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures.

Besides age, smoking is the most important risk factor for bladder cancer (see Section 4.2). Bove *et al*. (2014a) used COPD as a proxy for smoking and concluded that the confounding effect of smoking in their study was consistent with other occupational health studies. They also noted that "HRs for other smoking-related diseases such as cardiovascular disease, and cancers of the bladder, esophagus, stomach, pancreas, and liver were <1.0 in the Camp Lejeune cohort." Similarly, Bove *et al*. (2014a) stated:

> Among the smoking-related diseases not known to be associated with solvent exposure, only COPD was elevated in the Camp Lejeune cohort with HR of 1.21. Using the HR for COPD to adjust for the possible confounding effects of smoking would reduce the HRs for the diseases of primary and secondary interest by approximately 17.5%.

It is notable that Bove *et al*. (2014a) pointed out the HR for bladder cancer was <1.0 (HR = 0.76, 95% CI: 0.34-1.71). While smoking increases the risk of bladder cancer, it does not increase the risk of all smoking-related diseases equally (American Lung Association, 2024). The degree to which smoking contributed to these smoking-related diseases in study participants is unknown. Because this is unknown, this Bove *et al*. (2014a) analysis is not informative with respect to the degree of confounding from smoking in the bladder cancer risk estimates.

In a similar vein, Bove *et al*. (2024a,b) conducted quantitative bias assessments of various cancers to assess the potential bias from smoking using "negative control diseases." The studies, however, did not conduct such an analysis for bladder cancer. For other outcomes, the bias estimates were based on a series of assumptions that were not validated, so the results are uninterpretable.

Finally, the amount of missing covariate data was not always reported, which limits the ability to fully interpret the results.

5.1.5 Temporality

All of the studies had documented exposures prior to the onset of disease, and Bove *et al*. (2014a,b, 2024b) appropriately considered disease latency by incorporating 10-year lags into some of their analyses. Bove *et al*. (2024a) did not consider disease latency in their analyses but noted that 75% of the deaths occurred more than 10 years after the water contamination ended. ATSDR (2018a) also did not consider disease latency in their analyses, but stated that "virtually all participants with a confirmed cancer of interest developed their cancers ten years or more after they were first stationed or worked at either base."

5.2 Study Results

5.2.1 Bove *et al*. (2014b)

Bove *et al*. (2014b) retrospectively evaluated bladder cancer deaths among 154,932 Marines and Navy personnel who were stationed at Camp Lejeune between 1975 and 1985 and potentially exposed to contaminated drinking water on base. Between 1979 and 2008, there were 11 bladder cancer deaths in this cohort, which was fewer than expected compared to the general US population (SMR = 0.84, 95% CI: 0.42-1.51). The risk of bladder cancer death was also lower in Camp Lejeune Marines and Navy personnel compared to 154,969 Marines and Navy personnel at Camp Pendleton (HR [10-yr-lag] = 0.76, 95% CI: 0.34-1.71).

Bove *et al*. (2014b) used groundwater fate and transport models provided in ATSDR (2007b) and ATSDR (2013) to estimate individual level exposures to TCE, PCE, benzene, vinyl chloride, and other chemicals in the Camp Lejeune cohort based on the residence location on base. As discussed in Section 5.1.2, the estimated water concentrations of these chemicals were not likely accurate or reliable.

Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune did not have a statistically significant increased risk of bladder cancer death associated with increasing cumulative exposure to any chemical (HR range: 0.52-1.07). Similarly, there was no statistically significant increased risk of bladder cancer death with increased cumulative exposure to any chemical when comparing those with low, medium, or high exposures to those with ≤1 µg/L-month in this Camp Lejeune cohort (HR range: 0.00-4.04). The risk estimates did not increase in a linear pattern for any chemical (*i.e*., the highest risk estimate was in the middle category of exposure). The authors also evaluated the exposure-response relationship using both continuous and $\log_{10}$ continuous cumulative exposure models for each chemical and bladder cancer mortality and reported positive, but not statistically significant, beta-coefficients.

5.2.2 Bove *et al*. (2014a)

Bove *et al*. (2014a) retrospectively evaluated bladder cancer deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985 and potentially exposed to contaminated drinking water on base. Between 1979 and 2008, there were two bladder cancer deaths in this cohort, which was fewer than expected compared to the general US population (SMR = 0.53, 95% CI: 0.06-1.92). The risk of bladder cancer death was also lower in Camp Lejeune civilian employees compared to 4,690 civilian employees at Camp Pendleton (HR [10-yr-lag] = 0.65, 95% CI: 0.12-3.65). The authors did not assess risk of bladder cancer mortality for specific chemicals because of the small number of cases.

5.2.3 ATSDR (2018a)

ATSDR (2018a) retrospectively evaluated bladder cancer incidence among 50,684 Marines and Navy personnel and 2,168 civilian employees who were stationed between 1975 and 1985 or employed at Camp Lejeune between 1972 and 1985 and potentially exposed to contaminated drinking water on base. A health survey was administered between 2011 and 2012 that collected information on bladder cancer and lifestyle and demographic factors. Between 1979 and 2008, there were 182 bladder cancer cases among Marines and Navy personnel at Camp Lejeune, which was more than expected compared to Camp Pendleton Marines and Navy personnel (OR = 1.64, 95% CI: 1.02-2.64), and 13 cases among civilian employees, which was similar to what was expected compared to civilian employees at Camp Pendleton (OR = 0.82, 95% CI: 0.37-1.84).

The categorized levels (low, medium, high) of TCE, benzene, vinyl chloride, and total VOCs for the Marines and Navy personnel analyses were almost completely correlated ($\gamma = 0.99$), so the results were only presented for TCE and PCE ($\gamma = 0.88$). Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune did not have a statistically significant increased risk of bladder cancer incidence associated with increasing cumulative exposure to TCE (OR range: 0.93-1.68). Similarly, there was no statistically significant increased risk of bladder cancer incidence with increased cumulative exposure to TCE when comparing those with medium or high exposures to those with low exposure in this Camp Lejeune cohort (OR range: 0.74-1.34), and there was no pattern of increasing risk with increasing exposure level (*i.e.*, the highest risk estimate was in the medium exposure category).

Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune had increasing bladder cancer risk with increasing PCE exposure, but the risk was only statistically significant for the highest category of cumulative exposure to PCE (OR = 2.07, 95% CI: 1.12-3.82). There was no statistically significant increased risk of bladder cancer incidence when comparing Marines and Navy personnel at Camp Lejeune with medium PCE exposures (OR = 0.99, 95% CI: 0.69-1.40) or high exposures (OR = 1.54, 95% CI: 0.99-2.41) to those with low exposure.

The correlation between TCE and PCE in the civilian exposure estimates was approximately equal to one, so the results were reported for TCE and PCE combined. There was no clear association between TCE and PCE and bladder cancer incidence among civilian employees. Compared to those at Camp Pendleton, civilian employees at Camp Lejeune had no statistically significant increased risk of bladder cancer incidence with any level or exposure (OR range = 0.32-1.81), and there was no linear pattern of increasing risk with increasing exposure (*i.e.*, those in the medium exposure category had a lower risk than those in the low exposure category). Similarly, there was no statistically significant increased risk of bladder cancer incidence when comparing civilian employees at Camp Lejeune with medium or high TCE and PCE exposures to those with low exposure (OR range: 0.32-1.78), and there was no linear pattern of increasing risk with increasing exposure (*i.e.*, those in the medium exposure category had a lower risk than those in the low exposure category). The risk of incident bladder cancer and benzene or vinyl chloride was not evaluated in the civilian employee population. As discussed in Section 5.1.2, the estimated water concentrations of benzene and other chemicals were not likely accurate or reliable.

5.2.4 Bove *et al*. (2024a)

Bove *et al*. (2024a) retrospectively evaluated bladder cancer mortality among 159,128 Marines and Navy personnel stationed or employed at Camp Lejeune between 1975 and 1985 and 7,332 civilians employed at Camp Lejeune between 1972 and 1985, all who had been potentially exposed to contaminated drinking water on base. Between 1979 and 2018, there were 137 bladder cancer deaths among Marines and Navy personnel at Camp Lejeune, which was less than expected compared to the US general population (SMR = 0.90, 95% CI: 0.76-1.07) and similar to that among Camp Pendleton Marines and Navy personnel (HR = 0.89, 95% CI: 0.71-1.11). There were 18 bladder cancer deaths among civilian employees, which was less than expected compared to the US general population (SMR = 0.85, 95% CI: 0.50-1.34) and similar to that in Camp Pendleton civilian employees (HR = 0.65, 95% CI: 0.34-1.26).

Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune who began active duty between 1975 and 1985 did not have a statistically significant increase in risk of bladder cancer death associated with any duration of assignment (HR range: 0.80-1.24), and there was no increase in risk with increasing duration of assignment (*i.e.*, the lowest risk was in the medium duration category). Similarly, compared to those at Camp Pendleton, civilian employees at Camp Lejeune did not have a statistically significant increased risk of bladder cancer death associated with any duration of employment (HR range:

0.45-1.76), and there was no increase in risk with increasing duration of employment (*i.e.*, the highest risk was in the lowest exposure category).

5.2.5 Bove *et al*. (2024b)

Bove *et al*. (2024b) retrospectively evaluated bladder cancer incidence among 154,821 Marines and Navy personnel who began service and were stationed at Camp Lejeune between 1975 and 1985, and 6,494 civilians employed at Camp Lejeune between 1972 and 1985, who had been potentially exposed to contaminated drinking water on base. Between 1996 and 2017, there were 444 bladder cancer cases among Marines and Navy personnel at Camp Lejeune, which was similar to the incidence among Camp Pendleton Marines and Navy personnel (HR = 1.09, 95% CI: 0.95-1.24). The results for bladder cancer subtypes (*i.e.*, PTCC, NPTCC, urothelial, malignant bladder, and *in-situ* bladder) were very similar to the results for all 444 urinary bladder cancers combined (HR range: 0.99-1.11). Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune did not have a statistically significant increase in risk of bladder cancer associated with any duration of assignment (HR range: 1.02-1.20). The results for each bladder cancer subtype based on duration of assignment were very similar to the results for all urinary bladder cancers combined.

There were 87 bladder cancer cases among civilian employees, which was similar to what would be expected compared to Camp Pendleton civilian employees (HR = 1.10, 95% CI: 0.81-1.50). The results examining risk of bladder cancer subtypes were similar to the results for all 87 urinary bladder cancers combined (HR range: 1.07-1.30). Compared to those at Camp Pendleton, civilian employees at Camp Lejeune did not have any statistically significant change in risk for bladder cancer associated with low/medium (HR = 1.18, 95% CI: 0.80-1.75) or high durations of employment (HR = 1.09, 95% CI: 0.69-1.71). Risks of bladder cancer subtypes based on duration of employment were very similar to the results for all urinary bladder cancers combined; risk was highest for those with the shortest employments and lowest for those with the longest employments for all types. Although all risk estimates were above 1, none of the results for bladder cancer subtypes based on duration of employment were statistically significant (HR range = 1.06-1.51).

5.3 Toxicology

No animal carcinogenicity or mechanistic studies have investigated exposures to Camp Lejeune drinking water. As discussed in Sections 6.2, 7.2, 8.2, and 9.2, respectively, toxicity studies of TCE, PCE, benzene, and vinyl chloride either do not support causation at all, or do not provide evidence for a casual association with bladder cancer at Camp Lejeune. I did not identify any chronic *trans*-1,2-DCE animal toxicity studies.

5.4 Exposure

TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE concentrations in the water supply at Camp Lejeune have been modeled by ATSDR (2007b, 2013). As noted in Section 5.1.2, these values are unreliable and biased high. Still, in its assessment of potential health effects from contaminated drinking water at Camp Lejeune, NRC (2009) stated:

> 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.

To calculate VOC exposures at Camp Lejeune, NRC (2009) stated:

> 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 activities 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.

Assuming a person was exposed to twice the highest measured TCE and PCE concentrations in drinking water at Camp Lejeune (2,800 and 400 µg/L, respectively), NRC (2009) calculated TCE and PCE exposure levels of 0.2 and 0.02 mg/kg-day, respectively. NRC (2009) did not calculate benzene, vinyl chloride, or *trans*-1,2-DCE exposure levels.

NRC (2009) noted, "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."

5.5 Conclusions

Five studies have evaluated bladder cancer risks among Marines or Navy personnel stationed at Camp Lejeune or civilian workers on base. There was variation among studies with respect to the methods used to recruit or assemble the study populations, characterize exposures, and address confounding. Overall, there were no consistent associations reported between either working or living at Camp Lejeune or TCE, PCE, benzene, or vinyl chloride exposures at Camp Lejeune and bladder cancer. Almost all risk estimates were statistically null and close to 1. The few reported statistically significant risk estimates were not reported across other analyses of the Camp Lejeune population. These studies all had several methodological limitations, including a high likelihood of exposure misclassification, no adjustment for smoking, and the potential for selection bias in ATSDR (2018a). There are no animal carcinogenicity or mechanistic studies of Camp Lejeune drinking water, but animal carcinogenicity and mechanistic studies do not provide evidence that exposures to TCE, PCE, benzene, or vinyl chloride can cause bladder cancer, and the epidemiology studies at Camp Lejeune do not demonstrate that being stationed or employed at Camp Lejeune or exposure to any individual chemical at Camp Lejeune, was sufficient to cause bladder cancer.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and toxicity studies do not provide evidence of causation in humans either at all or at relevant exposure concentrations, I conclude that, as a whole, evidence does not support a causal association between being stationed or employed at Camp Lejeune, or exposure to TCE, PCE, benzene, or vinyl chloride in drinking water at Camp Lejeune, and bladder cancer.

6 TCE and Bladder Cancer

In this section, I describe epidemiology and toxicity studies that assessed TCE exposure and bladder cancer, and government and other agency reviews of this evidence. I conclude that scientific evidence does not support a causal association between TCE and bladder cancer.

6.1 Epidemiology

6.1.1 Overview

I identified 32 cohort studies (in 24 unique populations), seven case-control studies, three pooled analyses, and one meta-analysis that evaluated TCE exposure and bladder cancer. Almost all study populations were from Europe and North America; two were from Taiwan. I review here all studies of populations at Camp Lejeune if TCE exposures were specified, even if overlapping, for completeness. If several studies analyzed the same cohorts or population groups, I summarize only the most recent study because it had longer follow-up times and/or used more reliable exposure estimates, unless older studies reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of study characteristics, below, and this is reviewed in more detail in Tables D.1 and D.3 for cohort and case-control studies, respectively. Study results are discussed briefly in Section 6.1.2 and reviewed in more detail in Tables D.2 and D.4. The pooled and meta-analyses are also summarized in Table D.5, and study quality is reviewed in more detail in Table C.1. Epidemiology evidence is integrated with experimental evidence in Section 6.3.

6.1.1.1 Study Population

In most cohort studies, exposed and unexposed participants were selected from the same source population. Individuals with and without bladder cancer were also drawn from appropriate source populations in most case-control studies, but a few used inappropriate control groups, which could have increased the risk of selection bias (*e.g.*, Siemiatycki *et al*. [1994] used cancer-based controls). Most cohort studies reported low exclusion rates (<20%), however, approximately one-third of the studies reported high (>20%) or unknown loss to follow-up. Most of the case-control studies reported low (<80%) or unknown participation rates among controls, which increased the potential for selection bias. In most cohort and case-control studies that reported high loss to follow-up or low participation rates, the authors did not report information on how those who were included differed from those who were not, making the assessment of selection bias difficult. As discussed in Section 5, ATSDR (2018a) noted that in its Camp Lejeune study, selection bias could have biased results away from the null.

6.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to TCE *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation of all cohort and case-control studies was the manner by which exposures were estimated. TCE exposure was estimated based on place of employment, job titles, a JEM, biomarkers, self-reported exposures, or the presence of TCE in drinking water or indoor air. Most of the studies estimated individual exposures to TCE in an indirect manner, usually based on a JEM, self-reported exposure, or occupational category. Except for the study by Hansen *et al*. (2001), which linked air sampling data to individuals, there were no directly measured air or water exposure concentrations linked to individuals in any studies. Several studies assessed urinary TCA (U-TCA) levels (including Hansen *et al*., 2001), but this direct measurement is only reflective of recent exposure and is not specific to TCE (ATSDR, 2019b).

Bove *et al*. (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on ATSDR (2007b, 2013) groundwater fate and transport models, along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). Neither of these studies had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014b) and ATSDR (2018a), which limits the interpretation of the TCE-specific results.

Most of the case-control studies characterized exposure based on self-reported exposure or occupational information collected after bladder cancer had been diagnosed (*e.g*., Pesch *et al*., 2000). Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between chemical use or exposure and interviews, and potential recall bias when cases may have recalled exposures differently than controls. Most of the studies did not consider the time-varying nature of potential exposures (*e.g*., exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

Most studies did not consider the frequency, duration, or intensity of potential exposures. The studies that did attempt to account for exposure conditions did so based on modeled contamination in drinking water (with no individual consumption data), a JEM, duration of employment, or U-TCA; these indirect measurements are often crude and generally do not reflect actual individual exposure levels.

6.1.1.3 Outcome Assessment

Information on bladder cancer outcomes was obtained or confirmed using reliable and complete methods in most cohort and case-control studies. Most cohort studies identified cases using medical records, registries, or government databases (*e.g*., a national death index), and most case-control studies identified cases from registries, national databases, or medical facilities. A few studies may have had incomplete ascertainment of cases, namely when relying on self-reporting to identify cases without another source of identification (such as a registry to identify cases who did not self-report or who were deceased, *e.g*., ATSDR [2018a]). Most studies reported on bladder cancer incidence or mortality specifically, but several studies reported on larger system-level cancers (*e.g*., cancers of the bladder, ureter, and urethra combined in Pukkala *et al*. [2009]), which did not provide an accurate estimate of the TCE/bladder cancer association. All studies had ≥5 years of follow-up.

6.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. Most studies controlled for age and sex, while other variables were controlled for less consistently (*e.g*., race, smoking). Smoking causes half of all bladder cancers, so the results of studies that

didn't consider smoking may not be reliable. Schoenberg *et al*. (1984) is the only study that controlled for prior cancer treatment, chronic bladder inflammation, and family history of bladder cancer; no studies controlled for genetic factors. Even when important covariate data were collected, none of the studies accounted for the time-varying nature of certain covariates in analyses (*e.g*., smoking). Most of the studies did not provide information on the degree or impact of missing covariate data.

6.1.1.5 Temporality

Most of the cohort studies assessed or considered exposures occurring prior to the outcome, but many did not ensure an adequate period of time between exposure and diagnosis (*i.e*., ≥4 years for bladder cancer; CDC [2015]), either in the design or the analysis. This may undermine the ability to properly assess an association, although in most instances, as noted above, there was a long enough duration of follow-up that this is likely not a large concern. Most of the case-control studies collected information on exposures after entry into the study, increasing the potential for recall bias. Most case-control studies appropriately considered a latency period.

6.1.2 Study Results

Cohort and case-control studies reported a range of risk estimates for TCE and bladder cancer incidence and mortality, but almost all were statistically null and most were around 1 (both above and below). Among the dozens of reported risk estimates across cohort studies, statistically significant increased risks were only reported by Morgan *et al*. (1998), Wilson *et al*. (2008), and Pukkala *et al*. (2009). Morgan *et al*. (1998) reported an increased risk of bladder cancer mortality among aircraft manufacturing workers categorized as having high cumulative TCE exposure when compared to unexposed workers (RR = 2.71, 95% CI: 1.10-6.65) but not when workers in the high exposure category were compared to the US population (SMR = 1.79, 95% CI: 0.72-3.69). Wilson *et al*. (2008) reported elevated SIRs in multiple occupational groups for males only, including machine and electronics industry (SIR = 1.13, 95% CI: 1.08-1.18), shop and construction work (SIR = 1.10, 95% CI: 1.06-1.15), machine assembly (SIR = 1.27, 95% CI: 1.11-1.45), and shop and metal industry work (SIR = 1.18, 95% CI: 1.05-1.33). Pukkala *et al*. (2009) reported an increased risk of incident bladder cancer among mechanics, electrical workers, painters, and printers in Denmark, Finland, Iceland, Norway, and Sweden (SIR range: 1.08-1.46). In all of these studies exposures were estimated indirectly based on occupation – Morgan *et al*. (1998) based on job classification and a JEM, and Wilson *et al*. (2008) and Pukkala *et al*. (2009) based on self-reported occupation in censuses. Neither study adjusted for smoking or other potentially important confounders beyond age and sex.

Case-control studies reported ORs and HRs in the range of 0.3-1.9, except for Siemiatycki *et al*. (1994). Siemiatycki *et al*. (1994) reported a large increased risk of bladder cancer incidence among textile dyers and finishers with ≥10 years of exposure (OR =10.8, 1.0-12.0) compared to unexposed workers, but this was based on only two exposed cases. When study participants were instead classified by "industry," workers in the textile industry with ≥10 years of exposure did not have an increased risk of bladder cancer (OR = 1.0, 95% CI: 0.4-2.3, n = 7) compared to unexposed workers. Among all case-control studies, only Hadkhale *et al*. (2017) reported statistically significant associations with bladder cancer incidence, with risks ranging from 0.93-1.27. This study relied on self-reported occupational history in decennial censuses and JEMs to estimate exposure, and did not adjust for smoking.

Several studies examined at least three levels of exposure based on dose, duration, or frequency, but there were no consistent dose-response findings reported within or across studies, and only one of these studies adjusted for smoking (Pesch *et al*., 2000). Zhao *et al*. (2005) found an increased risk of bladder cancer incidence with increasing exposure with no exposure lag, but this was not the case for mortality or when a

20-year lag was included in the model. There were no trends of increased risk of bladder cancer incidence or mortality with increased cumulative exposure to TCE in the Camp Lejeune studies (ATSDR, 2018a; Bove *et al*., 2014b). Among case-control studies, only Pesch *et al*. (2000) and Hadkhale *et al*. (2017) evaluated dose-response; Pesch *et al*. (2000) found no increased risks with increasing exposure, while Hadkhale *et al*. (2017) reported a significant positive trend for males, but not females or all participants, and not when analyses were stratified by age of diagnosis <50 or ≥50 years.

Only one study examined TCE exposure and urothelial carcinoma (Pesch *et al*., 2000). Pesch *et al*. (2000) conducted a multicenter population-based case-control study in five regions in Germany. There was no increased risk of incident urothelial cancer with increasing exposure for either males or females using a German JEM. However, there was an increased risk among males in the substantial exposure group (>90th percentile of duration of exposure among exposed controls) using a job task exposure matrix (JTEM) (OR = 1.8, 95% CI: 1.2-2.7). The authors did not report results for females using the JTEM.

I identified one meta-analysis (Wartenberg *et al*., 2000) and three pooled studies (Kogevinas *et al*., 2003; Hansen *et al*., 2013; Sciannameo *et al*., 2018) that examined TCE and bladder cancer. Over 20 years ago, Wartenberg *et al*. (2000) reported an increased risk of bladder cancer mortality (SMR = 2.0, 95% CI: 1.3-2.9) in dry-cleaning and laundry workers. This observation was based on four cohort studies classified as lower quality, as Wartenberg *et al*. (2000) indicated that subjects were exposed to a variety of solvents including TCE. Kogevinas *et al*. (2003) evaluated bladder cancer risk by occupation and reported an increased risk of bladder cancer incidence among automobile mechanics (OR = 1.38, 95% CI: 1.02-1.87) and printers and related workers (OR = 1.45, 95% CI: 1.07-1.97), but not in launderers, dry-cleaners, or pressers, metal processers, or textile workers. Hansen *et al*. (2013) pooled data from cohorts with documented exposure to TCE and reported no increased risk of bladder cancer among those exposed (SIR = 1.17, 95% CI: 0.75-1.26). Sciannameo *et al*. (2018) reported no increased risk of bladder cancer incidence in their pooled analysis of two Italian case-control studies (OR [ever exposed] = 1.21, 95% CI: 0.98-1.50). Kogevinas *et al*. (2003) and Wartenberg *et al*. (2000) relied on occupational data to classify exposures, while Hansen *et al*. (2013) used U-TCA, which is not specific to TCE and does not reflect long-term exposures. The meta- and pooled analyses cannot overcome limitations in the original research studies, particularly exposure misclassification, and did not include several studies published after they were conducted.

Xie *et al*. (2024) evaluated TCE, PCE, and benzene exposures and bladder cancer risk. This study was discussed by Plaintiffs' experts but was published after I completed my literature search (Attachment A). Xie *et al*. (2024) used data from the New England Bladder Cancer Study (NEBCS), a population-based case-control study that evaluated the incidence of urothelial cell carcinoma of the bladder between 2001 and 2004, and estimated chemical exposures using self-reported occupational histories and a JEM. None of the participants were exposed to TCE so risks were not assessed. The authors reported that participants with any PCE exposure had a decreased risk of bladder cancer (OR = 0.36, 95% CI: 0.13-0.96) and those who were ever exposed benzene had an increased risk of bladder cancer (OR = 1.63, 95% CI: 1.14-2.32), but there was no evidence of dose-response (p_{trend} = 0.14). Like many other bladder cancer studies I reviewed in my report, this study had several methodological limitations, including a high likelihood of exposure misclassification and residual and uncontrolled confounding, and low participation rates (65% participation in cases and controls).

6.1.3 Conclusions

Most cohort and case-control studies did not report associations between TCE exposure overall and bladder cancer or any dose-response relationships. All of these studies had critical methodological limitations that impact the interpretation of the results, particularly with respect to exposure measurements, and most

studies did not adjust for smoking or other potentially important confounders besides age and sex. I conclude that the epidemiology evidence does not support a causal association between TCE exposure and bladder cancer.[8]

6.2 Toxicology

6.2.1 Animal Carcinogenicity Studies

I identified ten oral and seven inhalation chronic bioassays that stated they evaluated TCE exposure and the bladder. The results of these studies are reported in Attachment E, Tables E.1 and E.2; an overview of chronic study quality is described in Attachment E, Table E.3, and the quality of individual chronic studies is shown in Attachment E, Table E.4. Experimental evidence is integrated with epidemiology evidence in Section 6.3.

Among the 10 chronic oral TCE bioassays in rats and mice, there were no increases in bladder tumor incidence in two NCI (1976) bioassays and two NTP (1990) bioassays. A few benign and malignant bladder tumors were observed in rats in four bioassays conducted by NTP (1988), but none were significantly elevated in any sex or species at any dose. NTP (1988) concluded, "The studies are considered inadequate for either comparing or assessing trichloroethylene-induced carcinogenesis in these strains of rats," due to "chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies." These deficiencies included many accidental deaths in the high-dose group due to gavage error. In the oral bioassays conducted by Henschler *et al.* (1984) and Maltoni *et al.* (1986, 1988a), the bladder was evaluated, but no bladder tumors were observed.

Seven inhalation bioassays evaluated bladder tumors. Henschler *et al*. (1980) observed a few benign and malignant bladder tumors in Wistar rats (but not in hamsters or mice of either sex) but concluded that they were not treatment-related. The exposure duration in this study was only 78 weeks, and the observation period was 156 weeks for rats and 130 weeks for mice and hamsters. Maltoni *et al*. (1986, 1988a) evaluated the bladder in several strains of rats and mice but did not report any bladder tumor incidence.

Overall, chronic bioassays had several methodological limitations, including inappropriate exposure and observation periods, and do not provide evidence that TCE can cause bladder cancer.

6.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which TCE could cause bladder cancer (US EPA, 2020c; ATSDR, 2019b; Zhu *et al*., 2024; Rusyn *et al*., 2014; NTP, 2021a). In humans and animals, TCE is metabolized *via* oxidation and glutathione conjugation, mainly in the liver and kidney, but also in the lung and testes (IARC, 2014a; Cichocki *et al*., 2016). Some TCE metabolites can enter systemic circulation and have been detected in urine; however, there is no evidence that the bladder is a site of TCE metabolite formation, and the liver and kidney have the highest concentrations of TCE metabolites due to local formation in these organs (IARC, 2014a).

While the major oxidative metabolites of TCE are not mutagenic in most studies, there is evidence that some reactive glutathione metabolites (*e.g*., dichlorovinyl cysteine, dichlorovinyl glutathione) are mutagenic, and they form the basis of the proposed genotoxic MoA for kidney cancer (US EPA, 2020c;

[8] The results of the study by Xie *et al*. (2024), which I identified after the completion of my literature search (Section 6.1.2), do not change my conclusions regarding TCE exposure and bladder cancer risk.

ATSDR, 2019b; IARC, 2014a; Cichocki *et al*., 2016). However, metabolism through the oxidation pathway greatly exceeds the glutathione conjugation pathway, and it remains unclear whether human metabolism through the minor glutathione pathway is sufficient to support this MoA for kidney cancer (Chiu *et al*., 2009; IARC, 2014a; Cichocki *et al*., 2016; US EPA, 2011, 2020c). In the kidney, reactive metabolite formation in rodents may be an order of magnitude greater than that in humans, with the evidence overall indicating faster metabolism through both the oxidative and glutathione conjugation pathways (US EPA, 2011, 2020c). In the liver, TCE is metabolized to chloral hydrate, a reactive intermediate that may be genotoxic. However, the data overall are considered insufficient to support any particular MoA for liver tumorigenesis (US EPA, 2020c).

Although MoAs have been proposed for liver and kidney cancer as a result of TCE exposure – including those involving reactive metabolites, genotoxicity, oxidative stress, inflammation, immune-mediated effects, and gene expression alterations – mechanistic evidence for other cancers, including bladder cancer, is limited (US EPA, 2020c; Zhu *et al*., 2024; Lash, 2024). Limited data from human occupational studies have suggested that TCE exposure may cause epigenetic changes such as altered DNA methylation (Phillips *et al*., 2019) and affect biomarkers and proteins related to inflammation and immunity (Lee *et al*., 2019a,b; NTP, 2021a; Hosgood *et al*., 2022; US EPA, 2020c; ATSDR, 2019b); however, the exact mechanisms by which TCE exposure may result in these alterations, whether these changes represent adverse effects, and any etiologic relevance to cancer risk, including to bladder cancer, are unknown.

Although there is uncertainty regarding the contribution of TCE genotoxicity to carcinogenicity in humans (US EPA, 2020c), scientific and regulatory agencies have concluded that there is sufficient evidence to support a genotoxic MoA for TCE and kidney cancer *via* the formation of reactive glutathione metabolites, but that the MoA for liver cancer is unclear, and there is insufficient evidence to support MoAs for other etiologically distinct cancers, including bladder cancer (ATSDR, 2019b; IARC, 2014a; US EPA, 2011, 2020c). Overall, there is no compelling or consistent evidence to support a biologically plausible MoA by which TCE could cause bladder cancer.

6.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated TCE and bladder cancer (see Sections 6.1 and 6.2). Most of the epidemiology studies had higher-quality study designs and outcome assessments and had low likelihoods of selection bias. Appropriate consideration of temporality, particularly with respect to a latency period, and control for potential confounders varied across studies, and no study sufficiently controlled for all important potential confounders, particularly smoking. Most importantly, although some studies used semi-quantitative exposure estimates, most did not directly assess TCE exposures, calling into question the validity of reported risk estimates. In addition to being limited in number, animal studies do not provide evidence for causation. Keeping study strengths and weaknesses in mind, I review the available evidence as a whole in the context of Bradford Hill's considerations in Table 6.1. I conclude that the evidence does not support a causal association between TCE and bladder cancer.

Table 6.1 Bradford Hill Assessment of TCE and Bladder Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between TCE exposure and bladder cancer in cohort and case-control studies.
Consistency	Most studies consistently reported weak risk estimates both above and below 1 and statistically null.
Specificity	The evidence does not support a specific relationship between TCE and bladder cancer.
Temporality	Temporality was adequately addressed in some cohort studies but not in most case-control studies.

Aspect	Analysis
Dose-Response	There were no consistent trends of increasing risk with increasing exposures across the studies that considered multiple exposure levels.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which TCE could cause bladder cancer.
Coherence	Collectively, the evidence does not support a causal association between TCE exposure and bladder cancer. Almost all associations between TCE and bladder cancer in cohort and case-control studies were around 1 (both above and below) and were statistically null, there were no consistent dose-response relationships across studies, and each epidemiology study had several methodological limitations that impacted the interpretation of its results. There is no evidence that TCE causes bladder cancer in animal models, and toxicokinetic and MoA studies do not support a biologically plausible MoA for bladder cancer.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to TCE with respect to bladder cancer risk.

Notes:
MoA = Mode of Action; TCE = Trichloroethylene.

6.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.7). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Most government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding TCE and bladder cancer causation (ATSDR, 2017a; IOM, 2003, 2015; US EPA, 2020c), or did not draw any conclusions (ATSDR, 2019a; IARC, 2014; NTP, 2021a). These agency assessments of TCE carcinogenicity are described below.

6.4.1 ATSDR

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "sufficient evidence for causation" for TCE and kidney cancer, NHL, and cardiac defects; "equipoise and

above evidence for causation" for TCE and multiple myeloma, all types of leukemia, liver cancer, Parkinson's disease, end-stage renal disease, and systemic sclerosis/scleroderma; and "below equipoise evidence for causation" for TCE and pancreatic cancer, prostate cancer, breast cancer, bladder cancer, esophageal cancer, rectal cancer, and brain/central nervous system cancers.

The conclusion for bladder cancer was based on findings of "only limited evidence of a positive association" in epidemiology studies (ATSDR, 2017a), including negative results among most occupational cohort studies, and inconsistent results among the few studies that reported an association. ATSDR (2017a) did not address animal or mechanistic studies of TCE and bladder cancer.

In its Toxicological Profile for TCE, ATSDR (2019b) stated that there is "strong evidence that trichloroethylene can cause kidney cancer in people and some evidence that it causes liver cancer and malignant lymphoma (a blood cancer)." ATSDR (2019a) further stated, "Lifetime exposure to trichloroethylene resulted in increased liver cancer in mice and increased kidney cancer in rats at relatively high exposure levels. There is some evidence for trichloroethylene-induced testicular cancer and leukemia in rats and lymphomas and lung tumors in mice." Several epidemiology studies that addressed TCE and bladder cancer were listed, but ATSDR (2019a) did not present any conclusions regarding an association, and did not discuss any animal or mechanistic data specific to bladder cancer.

6.4.2 NASEM

Subcommittees of NASEM reviewed the associations between solvent exposures and various cancers in the contexts of the Gulf War and Camp Lejeune. Most of the studies included in NASEM's reviews were not specific to TCE. The Institute of Medicine (IOM), now called the National Academy of Medicine (NAM) and one of three NASEM operating units, conducted the first evaluation of insecticides and solvents in the context of the Gulf War (IOM, 2003). In 2003, IOM (2003) did not conclude that TCE was associated with any cancer type in humans.

IOM (2003) identified three cohort studies in which workers were biologically monitored for exposure to TCE; none showed an association with bladder cancer (Anttila *et al*., 1995; Axelson *et al*., 1994; Hansen *et al*., 2001). IOM (2003) also identified a nested case-control study, in which worker exposures were estimated based on job records, that also showed no association (Greenland *et al*., 1984). Other studies that IOM (2003) considered to have reasonably good assessments of solvent exposure included Gerin *et al*. (1998), Pesch *et al*. (2000), Aschengrau *et al.* (1993), Cordier *et al*. (1993), and Silverman *et al*. (1989a,b). IOM (2003) considered the findings for associations of TCE and bladder cancer "weak and imprecise," and noted that "[m]ost suffered from low statistical power and probable exposure misclassification." On this basis it concluded that there was "insufficient evidence to determine whether an association exists." IOM (2003) did not discuss any animal or mechanistic data.

In an assessment of potential health effects at Camp Lejeune, the National Research Council (NRC, 2009), the operating and principal programmatic arm of NASEM, concluded that there was "limited/suggestive evidence of an association" for TCE and kidney cancer in humans, but "inadequate/insufficient" evidence for other cancers evaluated. NRC (2009) also noted, "TCE was reported to cause kidney and testicular cancers in rats and liver and lung cancers in mice." The NRC (2009) conclusion was based on an updated review with four additional cohort studies of workers potentially exposed to TCE (Raaschou-Nielsen *et al*., 2003; Zhao *et al.*, 2005; Boice *et al.*, 2006; Sung *et al.*, 2007) and one that did not make a distinction between TCE and PCE (Chang *et al*., 2003). NRC (2009) also identified additional studies of dry-cleaning workers (Blair *et al*., 2003; Lynge *et al*., 2006) and a drinking water study (Morgan and Cassady, 2002). NRC (2009) noted that these newly identified studies had mixed and inconsistent results with respect to bladder cancer. Based on this analysis, NRC (2009) reiterated the conclusion from IOM (2003) that there

was "insufficient evidence to determine whether an association exists." NRC (2009) did not discuss any animal or mechanistic studies regarding TCE and bladder cancer.

In 2012, the US Congress passed the Honoring America's Veterans and Caring for Camp Lejeune Families Act, also known as the Janey Ensminger Act (Public Law 112-154) (IOM, 2015). The Veterans Health Administration (VHA) drafted clinical guidance to help determine which medical conditions should be covered by the act. IOM (2015) conducted and published a "Review of the VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation." In its 2015 review, the IOM committee identified four additional studies of solvent exposure and bladder cancer that had been published since the NRC (2009) report (Christensen *et al*., 2013; Hansen *et al*., 2013; Lipworth *et al*., 2011; Scott and Jinot, 2011) and stated, "These new studies have generally supported the conclusions of the previous report" (IOM, 2015). IOM (2015) did not cite any animal or mechanistic data regarding TCE and bladder cancer.

6.4.3 US EPA

US EPA (2011) has characterized TCE as "carcinogenic in humans by all routes of exposure," based on "convincing evidence of a causal association between TCE exposure in humans and kidney cancer." US EPA (2011) stated that evidence from epidemiology studies "is strong for non-Hodgkin Lymphoma but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer." US EPA (2011) further stated, "less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia." Regarding evidence from animal studies, US EPA (2011) noted chronic TCE exposure caused "low, but biologically and sometimes statistically significant, increases in the incidence of kidney tumors" and "statistically significant increases in TCE-induced liver tumors" in mice (but not rats or hamsters). US EPA (2011) concluded, "there is more limited evidence for TCE-induced lymphohematopoietic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats."

US EPA (2011) reviewed 25 epidemiology studies that evaluated TCE and bladder cancer. Thirteen studies were considered by US EPA to meet certain study design standards, including a high likelihood of TCE exposure in study subjects. Of these, seven reported a significant association at the highest exposure level and/or an increasing risk of bladder cancer with increasing exposure (Siemiatycki, 1991; Boice *et al.*, 2006; Morgan *et al*., 1998; Pesch *et al*., 2000; Radican *et al*., 2008; Zhao *et al.*, 2005; Blair *et al*., 1998). Twelve other studies were given less weight by US EPA (2011) due to a lesser likelihood of TCE exposure and other study design limitations. Based on this evaluation, US EPA (2011) stated, "the available epidemiologic studies also provide suggestive evidence of an association between TCE exposure and other types of cancer, including bladder." US EPA (2011) did not discuss animal or mechanistic data regarding TCE and bladder cancer.

In its most recent evaluation of TCE, US EPA (2020c) upheld its conclusion that TCE is "Carcinogenic to Humans" based on "positive associations of NHL, kidney cancer and liver cancer with exposure to TCE." Regarding bladder cancer, US EPA (2020c) stated, "There is some evidence of association for bladder or urothelial cancer and high cumulative TCE exposure, however the reasonably available studies examine multiple sites and do not completely account for potential confounding factors." US EPA (2020c) did not discuss any animal or mechanistic evidence for bladder cancer.

6.4.4 IARC

In 2014, IARC evaluated TCE and cancer and concluded TCE is "carcinogenic to humans (Group 1) (IARC 2014)." Regarding epidemiology evidence, IARC (2014) concluded there is "sufficient evidence" in humans that TCE "causes cancer of the kidney," and that there is a "positive association" with liver cancer

and NHL. Regarding evidence in experimental animals, IARC (2014) indicated that TCE caused liver and kidney cancer.

IARC (2014a) described 12 cohort, two case-control, and two ecological studies of TCE exposure and bladder cancer, but did not evaluate these studies. IARC (2014a) did not discuss animal or mechanistic data or make a determination regarding TCE and bladder cancer.

6.4.5 NTP

In its 2015 Report on Carcinogens Monograph on Trichloroethylene, NTP (2015) conducted a cancer hazard assessment focused on kidney cancer, NHL, and liver cancer. NTP (2015) classified TCE as "known to be a human carcinogen," based on "sufficient evidence of carcinogenicity from studies in humans." NTP (2015) stated, "This conclusion is based on epidemiological studies showing that TCE causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans." NTP (2015) did not discuss TCE and bladder cancer, but noted that, "IARC [2014] concluded that although cancer incidence was increased at several other tissue sites [*i.e.*, other than kidney, lymphohematopoietic system, and liver], the data were insufficient for an evaluation."

In its most recent evaluation of TCE, NTP (2021a) reaffirmed its previous classification of TCE as "known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans." NTP (2021a) stated:

> This conclusion is based on epidemiological studies showing that it causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence that trichloroethylene causes non-Hodgkin lymphoma (NHL) in humans. Supporting evidence is provided by studies in experimental animals demonstrating that trichloroethylene causes cancer at several tissue sites, including some of the same sites as seen in humans.

Regarding evidence from experimental animal studies, NTP (2021a) stated that TCE caused kidney and testicular tumors in male rats, liver and lung tumors in mice of both sexes, and lymphoma in female mice. NTP (2021a) did not discuss TCE and bladder cancer.

6.4.6 Conclusions

Most government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding TCE and bladder cancer causation (ATSDR, 2017a; IOM, 2003, 2015; US EPA, 2020c), or did not draw any conclusions (ATSDR, 2019a; IARC, 2014; NTP, 2021a). These determinations were based on a limited number of epidemiology studies with inconsistent results. None of the agencies presented any animal or mechanistic evidence regarding TCE and bladder cancer. US EPA (2011) was the only agency to conclude that there was "suggestive evidence of an association" based on a few epidemiology studies, but the agency did not present any supporting animal or mechanistic evidence and later acknowledged that "reasonably available studies examine multiple sites and do not completely account for potential confounding factors" (US EPA, 2020c).

6.5 Conclusions

Most government and scientific agencies have either concluded that the scientific evidence is insufficient to make a determination regarding TCE and bladder cancer causation (ATSDR, 2017a; IOM, 2003, 2015; US EPA, 2020c), or have not drawn any conclusions (ATSDR, 2019a; IARC, 2014; NTP, 2021a). These determinations were based on a limited number of epidemiology studies with inconsistent results, and none of the agencies presented any animal or mechanistic evidence regarding TCE and bladder cancer. The majority of the associations between TCE and bladder cancer in epidemiology studies I reviewed were null and many were based on a small number of cases or were statistically unstable (based on wide CIs). There was no compelling evidence that supports a dose-response relationship, and each study had several methodological limitations that impacted the interpretation of the results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). There is no animal evidence indicating TCE can cause bladder cancer, or any proposed MoA with sufficient scientific support.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans, and (3) there is no MoA with sufficient scientific support, I conclude that, as a whole, scientific evidence does not support a causal association between TCE and bladder cancer.

7 PCE and Bladder Cancer

In this section, I describe epidemiology and toxicity studies that assessed PCE exposure and bladder cancer and governmental and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between PCE and bladder cancer.

7.1 Epidemiology

7.1.1 Overview

I identified 22 cohort studies (in 13 unique populations), 21 case-control studies, 2 pooled analyses, and 2 meta-analyses that evaluated PCE exposure and bladder cancer. Most of these studies were conducted in Europe and North America; two were conducted in Taiwan and one in New Zealand. I review here all studies in populations at Camp Lejeune where PCE exposures were specified, even if overlapping, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the most recent study because it had longer follow-up times and/or used more reliable exposure estimates, unless older studies reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of study characteristics and quality, below; this is reviewed in more detail in Tables C.1, F.1, and F.3. Study results are discussed briefly in Section 7.1.2 and reviewed in more detail in Tables F.2 and F.4; the pooled and meta-analyses results are reviewed in Table F.5. Epidemiology evidence is integrated with experimental evidence in Section 7.3.

7.1.1.1 Study Population

In most cohort studies, exposed and unexposed participants were selected from the same source population. Individuals with and without bladder cancer were also drawn from appropriate populations in most case-control studies. Several case-control studies selected controls from populations that were not representative of the population from which the cases were drawn and could have been subject to selection bias (*e.g.*, Christensen *et al*. [2013] used electoral lists where voter registration was non-compulsory to identify controls). There was a lot of variation in reporting on retention among cohort studies, but among those that did report on retention, all had low rates of loss to follow-up (<20%). Many of the case-control studies reported low (<80%) or unknown participation rates in cases and/or controls, which increased the potential for selection bias. In most cohort and case-control studies that reported high loss to follow-up or low participation, the authors did not report on how those who were included differed from those who were not, making the assessment of selection bias difficult. As discussed in Section 5, ATSDR (2018a) noted that in its Camp Lejeune study, selection bias could have biased results away from the null.

7.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to PCE *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption. The most critical limitation of all cohort and case-control studies was the manner by which exposures were estimated. The cohort studies examining PCE exposure and bladder cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, dry-cleaning workers).

All studies estimated PCE exposure in an indirect manner based on place of employment, job titles, a JEM, self-reported exposures, or the presence of PCE in drinking water (Camp Lejeune studies). There were no directly measured air or water exposure concentrations at the individual level in any studies.

Bove *et al*. (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007b, 2013) along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). Neither Bove *et al*. (2014b) nor ATSDR (2018a) had individual water consumption data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014b) and ATSDR (2018a), which limits the interpretation of the PCE-specific results.

Most of the case-control studies characterized exposure based on self-reported exposure or occupational information collected after bladder cancer had been diagnosed (*e.g*., Burns and Swanson, 1991). Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between potential chemical exposure and interviews, and potential recall bias when cases may recall exposures differently than controls.

Most of the studies did not consider the frequency, duration, or intensity of potential exposures. The studies that did attempt to account for dose did so based on modeled contamination in drinking water (with no individual consumption/exposure data), JEMs, or duration of employment; these indirect measurements are often crude and generally do not reflect actual individual exposure levels. In addition, most of the studies did not consider the time-varying nature of potential exposures (*e.g*., exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

7.1.1.3 Outcome Assessment

Information on bladder cancer outcomes was obtained or confirmed using reliable and complete methods in most cohort and case-control studies. Most cohort studies identified cases using medical records, registries, or government databases (*e.g*., national death index), and most case-control studies identified cases from registries, national databases, or medical facilities. A few studies may have had incomplete ascertainment of cases, namely when relying on self-reporting to identify cases without another source of identification (such as a registry to identify cases who did not self-report or who were deceased, *e.g*., ATSDR [2018a]). Most studies reported on bladder cancer incidence or mortality specifically, but several studies reported on larger system-level cancers (*e.g*., cancers of the bladder, ureter, and urethra combined in Pukkala *et al*. [2009]), which did not provide an accurate estimate of the PCE/bladder cancer association. All studies had sufficient follow-up time (*i.e*., >5 years).

7.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. Most studies controlled for age and sex, while other variables were controlled for less consistently (*e.g*., race, smoking). This is particularly an issue for smoking, which causes half of all bladder cancers in the US (see Section 4.2). Very few studies controlled for prior cancer treatment (Schoenberg *et al*., 1984; Teschke *et al*., 1997), chronic bladder inflammation (Schoenberg *et al*., 1984; Teschke *et al*., 1997), or family history of bladder cancer (Zheng *et al*., 2002), and no studies controlled for genetic factors. Even when important covariate data were collected, most of the cohort studies did not account for the time-

varying nature of relevant covariates in analyses (*e.g.*, smoking). Most of the studies did not provide information on the degree or impact of missing covariate data.

7.1.1.5 Temporality

All of the cohort studies assessed or considered exposures occurring prior to the outcome, but many did not ensure an adequate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥4 years for bladder cancer; CDC [2015]). Many studies appeared to include cases in the analysis that could have occurred <4 years after the exposure began, undermining the ability to properly assess an association, although in most instances, there was a long enough duration of follow-up that this is likely not a large concern. Most of the case-control studies collected information on exposures after entry into the study, increasing the potential for recall bias. Most case-control studies appropriately considered a latency period.

7.1.2 Study Results

Overall, cohort and case-control studies reported a wide range of risk estimates for PCE and bladder cancer, but most were around 1 (both above and below). Three cohort studies (Calvert *et al.*, 2011; ATSDR, 2018a; Callahan *et al.*, 2019) and eight case-control studies (Smith *et al.*, 1985; Silverman *et al.*, 1989a,b; Silverman *et al.*, 1990; Pesch *et al.*, 2000; Lynge *et al.*, 2006; Reulen *et al.*, 2007; Hadkhale *et al.*, 2017) reported statistically significant results. All but Silverman *et al.* (1989a) reported positive associations. Most of these studies were based on employment in a specific occupation (*e.g.*, dry-cleaning/laundry) or active duty/employment at Camp Lejeune. Seven of these studies (Calvert *et al.*, 2011; ATSDR, 2018a; Callahan *et al.*, 2019; Silverman *et al.*, 1990; Pesch *et al.*, 2000; Lynge *et al.*, 2006; Hadkhale *et al.*, 2017) reported statistically significant results that considered exposure dose, duration, or frequency. All seven studies reported statistically significant and positive associations, but there were no consistent dose-response relationships reported across or within these studies.

Calvert *et al.* (2011) analyzed cancer risk in US dry-cleaners. The study reported a statistically significant increase in cancer mortality associated with bladder and other urinary organs among those with ≥20 years since first employment and ≥5 years of duration (SMR = 4.08, 95% CI: 2.13-7.12) when compared with the US general population. In addition, there was an increase in bladder cancer mortality in workers in the PCE-plus group (*i.e.*, worked in PCE-only shops and shops mainly using other solvents) compared to the US general population (SMR = 2.59, 95% CI: 1.24-4.76). Notably, all deaths occurred among those who also worked in shops mainly using other solvents in addition to PCE and no deaths occurred among those with ≥5 years of employment duration but less than 20 years since first employment. Callahan *et al.* (2019) observed an increase in bladder cancer mortality among dry-cleaning workers with high PCE exposure (HR [20-yr latency] = 9.2, 95% CI: 1.1-76.7) when compared with workers with no or low PCE exposure, though this estimate was based on only three deaths. In a European study of dry-cleaners in small shops (*i.e.*, <10 workers), Lynge *et al.* (2006) observed an increased risk of bladder cancer incidence among workers with 2-4 years (RR = 2.39, 95% CI: 1.09-5.22) or ≥10 years (RR = 1.57, 95% CI: 1.07-2.29) of employment, but not among workers with 5-9 years of employment (RR = 0.91, 95% CI: 0.52-1.59). In a large European study, Hadkhale *et al.* (2017) observed an increased risk of bladder cancer incidence among those participants with an occupational cumulative exposure of 13.60 to 87.55 ppm PCE (HR [10-yr lag] = 1.12, 95% CI: 1.02-1.23), but not among those with exposure to >87.55 ppm PCE (HR [10-yr lag] = 0.94, 95% CI: 0.73-1.22) or in analyses stratified by age or sex.

Only one study, Silverman *et al.* (1990), reported statistically significant exposure-response trends. They reported decreasing risks with increasing duration of employment in metal fabrication, assembly, and repair work as well as textile workers. However, these relationships were not specific to PCE exposure.

ATSDR (2018a) reported a statistically significant increased risk among Camp Lejeune Marines and Navy personnel compared to Camp Pendleton (OR = 1.64, 95% CI: 1.02-2.64), but not for civilian employees (OR = 0.82, 95% CI: 0.37-1.84), though these results were again not specific to PCE exposure. A statistically significant increase in risk was observed for those with high PCE exposure (OR = 2.07, 95% CI: 1.12-3.82) among Marines and Navy personnel when compared with Camp Pendleton, though this association did not persist in internal analyses.

There were three case-control studies that specifically investigated the risk of urothelial cancer among individuals exposed to PCE (Steineck *et al*., 1990; Pesch *et al*., 2000; Colt *et al*., 2011). In a study of incident urothelial cancer in Stockholm, Sweden, Steineck *et al*. (1990) reported that dry-cleaners did not have increase in risk compared to people not employed as dry-cleaners (RR = 1.2, 95% CI: 0.2-9.2). In their population-based case-control study in Northern New England, Colt *et al*. (2011) also did not observe a difference in risk of incident urothelial carcinoma of the bladder among launderers and dry-cleaners when compared to those never employed in that occupation/industry (ORs ranged from 0.30 to 2.19 depending on sex and specific occupation, with no statistically significant results). Pesch *et al*. (2000) observed an increased risk of urothelial cancer incidence among German men with substantial duration of exposure (>90th percentile) to PCE (OR = 1.8, 95% CI: 1.1-3.1), compared with individuals with low exposure to PCE (<30th percentile of duration of exposure). This observation was based on a job task-exposure matrix (JTEM) developed by the authors to account for regional differences in Germany and temporal changes in occupational exposure. When a pre-designed German JEM was used to estimate exposure, this association was not significant (OR = 1.4, 95% CI: 1.0-1.9).

I identified two meta-analyses (Reulen *et al.*, 2008; Vlaanderen *et al*., 2014) and two pooled studies (Kogevinas *et al*., 2003; Sciannameo *et al*., 2018) that estimated the association between PCE exposure and bladder cancer (Table F.5). All studies besides Sciannameo *et al*. (2018) examined risks among occupational groups (*e.g*., launderers and dry-cleaners) rather than by levels of PCE exposure. Most reported risk estimates were close to 1 (range: 0.79-1.72). Reulen *et al*. (2008) examined risks in launderers and reported a statistically significant increased risk of bladder cancer incidence based on case-control studies only (OR = 1.66, 95% CI: 1.23-2.24) and in studies that adjusted for smoking (OR = 1.72, 95% CI: 1.25-2.37). However, the authors also reported statistically significant between-study heterogeneity for these analyses and there were no associations observed in analyses involving all studies combined (OR = 1.27, 95% CI: 0.95-1.71) or only cohort studies (OR = 0.82, 95% CI: 0.54-1.25). Vlaanderen *et al*. (2014) reported a statistically significant increased risk of bladder cancer in laundry and dry-cleaning workers when considering all cohort and case-control studies (RR = 1.20, 95% CI: 1.06-1.36) combined. They also reported an increased risk in analyses limited to case-control studies (RR = 1.54, 95% CI: 1.17-2.04) but, similar to Reulen *et al*. (2008), not in analyses limited to cohort studies (RR = 1.17, 95% CI: 0.95-1.44). Kogevinas *et al*. (2003) did not report any statistically significant increased risks of bladder cancer among launderers, dry cleaners, and pressers (OR = 1.24, 95% CI: 0.67-2.31) or textile workers (OR = 1.05, 95% CI: 0.81-1.36), and Sciannameo *et al*. (2018) did not report increased risks among those ever exposed in their pooled analysis of two Italian case-control studies (OR = 1.04, 95% CI: 0.56-1.91) or among those with ≥ median cumulative exposure (OR = 0.79, 95% CI: 0.31-1.97). In addition, because all the studies used in these analyses relied on indirect exposure assessments in primary studies, the meta- and pooled analyses cannot overcome the critical limitation of the potential for exposure misclassification.

7.1.3 Conclusions

Most cohort and case-control studies did not report associations between PCE exposure and bladder cancer or demonstrate exposure-response relationships. All studies had critical methodological limitations that impact the interpretation of their results, particularly with respect to exposure measurements, and most

studies did not adjust for certain relevant covariates (*e.g.*, smoking). I conclude that the epidemiology evidence does not support a causal association between PCE exposure and bladder cancer.[9]

7.2 Toxicology

7.2.1 Animal Carcinogenicity Studies

I identified two oral and four inhalation chronic bioassays that stated they evaluated PCE exposure and the bladder. The results of these chronic studies are reported in Attachment G, Tables G.1 and G.2; an overview of chronic study quality is described in Attachment G, Table G.3; and the quality of individual chronic studies is shown in Attachment G, Table G.4. Experimental evidence is integrated with epidemiology evidence in Section 7.3.

The two chronic oral PCE bioassays were conducted by NCI (1977). Bladder tumors were not observed in either Osborne-Mendel rats or B6C3F1 mice. The agency noted that, "[B]ecause of a high rate of early deaths in treated rats the results of this bioassay do not allow an evaluation of the carcinogenicity of [PCE]." Of the four chronic inhalation PCE bioassays, a few benign and malignant bladder tumors were observed in F344/N rats in one bioassay conducted by NTP (1986b) but the incidences were not statistically different than controls. No bladder tumors were reported for rats or mice in the other three bioassays (NTP, 1986b; JISA, 1993). Collectively, chronic PCE oral (NCI, 1977) and inhalation studies (NTP, 1986b; JISA, 1993) do not provide evidence that PCE can cause bladder cancer.

7.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which PCE could cause bladder cancer (IARC, 2014b; US EPA, 2020a; ATSDR 2019a; Cichocki *et al*., 2016). Animal and human studies indicate that PCE metabolism is relatively limited, particularly at higher exposures (US EPA, 2012, 2020a), but it can occur *via* both oxidation and glutathione conjugation pathways, mainly in the liver and kidney, but also in the lung (US EPA, 2012, 2020a; IARC, 2014b; Cichocki *et al*., 2016). Some PCE metabolites can enter systemic circulation and have been detected in urine; however, there is no evidence that the bladder is a site of PCE metabolite formation, and the liver and kidney have the highest relative concentrations of PCE metabolites due to local formation in these organs (IARC, 2014b).

In both humans and animals, metabolism through the oxidation pathway exceeds the conjugation pathway, and the major oxidative metabolites of PCE are not mutagenic in most studies. In contrast, there is evidence that some glutathione conjugation metabolites of PCE are mutagenic (IARC, 2014b; Cichocki *et al*., 2016), and they form the basis of the potential mutagenic MoA for kidney cancer as a result of PCE exposure. However, substantial uncertainty exists regarding the contribution of the glutathione conjugation pathway to PCE metabolism, including the extent to which humans form reactive glutathione metabolites (US EPA, 2012, 2020a; Chiu and Ginsberg, 2011; IARC, 2014b; Cichocki *et al*., 2016).

Limited data from immunotoxicity studies have suggested that PCE exposure may increase oxidative stress and alter white cell counts and immune system markers in humans and mice (US EPA, 2012, 2020a; Li *et al*., 2024; Ghahri *et al*., 2022), but some of these changes were observed at cytotoxic concentrations and reported effects were inconsistent across studies (*e.g.*, both anti-inflammatory and inflammatory changes

[9] The results of the study by Xie *et al*. (2024), which I identified after the completion of my literature search (Section 6.1.2), do not change my conclusions regarding TCE exposure and bladder cancer risk.

were observed). Whether immune system alterations are involved in carcinogenicity induced by PCE is unknown (ATSDR 2019a; US EPA, 2020a).

Scientific and regulatory agencies have concluded that there is some evidence to support potential MoAs for PCE and liver and kidney cancer (although evidence is insufficient to establish definitive MoAs), but not other cancer types, including bladder cancer (ATSDR, 2019a; IARC, 2014b; US EPA, 2012, 2020a). Overall, there is no compelling or consistent evidence to support a biologically plausible MoA by which PCE could cause bladder cancer.

7.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated PCE and bladder cancer (see Sections 7.1 and 7.2). Most of the epidemiology studies had higher-quality study designs and outcome assessments and had low likelihoods of selection bias. Appropriate consideration of temporality, latency period, and control for potential confounders varied across studies, and no study sufficiently controlled for all important potential confounders, particularly smoking. Most importantly, none of the studies directly assessed individual PCE exposures, calling into question the validity of reported risk estimates. In addition to being limited in number, animal studies do not provide evidence for causation. Keeping study strengths and weaknesses in mind, I review the available evidence as a whole in the context of Bradford Hill's considerations in Table 7.1. I conclude that the evidence does not support a causal association between PCE and bladder cancer.

Table 7.1 Bradford Hill Assessment of PCE and Bladder Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between PCE exposure and bladder cancer in cohort and case-control studies.
Consistency	Epidemiology studies did not report consistent associations between PCE exposures and bladder cancer. Most cohort studies reported statistically null results while case-control studies reported weak risk estimates greater than but close to 1.
Specificity	The evidence does not support a specific relationship between PCE and bladder cancer.
Temporality	Temporality was adequately addressed in some cohort studies but not in most case-control studies.
Dose-Response	There were no consistent trends of increasing risk with increasing exposures across the studies that considered multiple exposure levels.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which PCE could cause bladder cancer.
Coherence	Collectively, the evidence does not support a causal association between PCE exposure and bladder cancer. Most of the associations between PCE and bladder cancer in epidemiology studies were statistically null and close to 1 (although generally >1 in case-control studies), there were no consistent dose-response relationships across studies, and each epidemiology study had several methodological limitations that impacted the interpretation of its results. PCE does not cause bladder cancer in animal models, and toxicokinetic and MoA studies do not support a biologically plausible MoA for bladder cancer.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to PCE with respect to bladder cancer risk.

Notes:
MoA = Mode of Action; PCE = Perchloroethylene.

7.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.7). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Most government and scientific agencies concluded there is some weak scientific evidence for an association between PCE and bladder cancer, but that the evidence is too limited to address causation (ATSDR, 2019b; IOM, 2003, 2015; US EPA, 2020a; IARC, 2014b; NTP, 2021b). These agency assessments of PCE carcinogenicity are described below.

7.4.1 ATSDR

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "sufficient evidence for causation" for PCE and bladder cancer, "equipoise and above evidence for causation" for PCE and NHL and end-stage renal disease, and "below equipoise evidence for causation" for PCE and kidney cancer, multiple myeloma, leukemias, liver cancer, pancreatic cancer, prostate cancer, breast cancer, Parkinson's disease, esophageal cancer, rectal cancer, brain/central nervous system cancers, systemic sclerosis/scleroderma, and cardiac defects.

ATSDR (2017a) based its conclusion regarding bladder cancer on a small increased risk in a meta-analysis by Vlaanderen *et al*. (2014), as well as an increased risk among dry-cleaning workers in a study by Blair *et al*. (2003),[10] and an exposure-response trend in a drinking water study by Aschengrau *et al.* (1993).[11] ATSDR (2017a) noted that there were no animal studies or strong mechanistic data that supported

[10] Callahan *et al*. (2019) added 22 years of follow-up to the Blair *et al*. (2003) study, and risks were not statistically significant in any analyses.
[11] The exposure-response trend was based on very few exposed cases in an unadjusted analysis. The estimated unadjusted risk in the high exposure category were based on only 4 exposed cases and was statistically unstable (OR = 6.04, 95% CI: 1.32-21.84).

causation, but cited some evidence suggesting that workers with certain genetic variations that affected one of the major metabolic pathways for PCE are at increased risk of bladder cancer.[12]

In its 2019 Toxicological Profile for PCE, ATSDR (2019b) stated, "Available human data provide suggestive, but weak evidence for [PCE]-induced non-Hodgkin's lymphoma, multiple myeloma, and bladder cancer in humans." Regarding evidence from animal studies, ATSDR (2019b) reported, "Increased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to tetrachloroethylene *via* inhalation and oral exposure routes."

ATSDR (2019b) relied on the US EPA (2012) criteria to identify what it considered to be 10 higher-quality cohort and five higher-quality case-control studies of dry-cleaning and other PCE-exposed workers that evaluated PCE exposure and bladder cancer. Based on the findings of these studies, ATSDR (2019b) concluded, "Available human data provide suggestive, but weak evidence for tetrachloroethylene-induced…bladder cancer in humans." ATSDR (2019b) did not discuss any animal or mechanistic studies of PCE and bladder cancer.

7.4.2 NASEM

In 2003, IOM (2003) did not conclude that PCE caused any cancer type in humans. It concluded there was "limited/suggestive evidence of an association between chronic exposure to tetrachloroethylene and dry-cleaning solvents and bladder cancer" (IOM, 2003) based mainly on two cohort studies of dry-cleaning workers that showed positive associations (Blair *et al*., 1990; Ruder *et al*., 2001), and several case-control studies that reported positive associations that were not statistically significant (Schoenberg *et al*., 1984; Teschke *et al*., 1997; Smith *et al*., 1985). IOM (2003) also considered a study of PCE in drinking water (Aschengrau *et al.*, 1993) and a worker study that showed an increased risk in men but not in women (Pesch *et al*., 2000). IOM (2003) did not cite any animal or mechanistic data.

In an assessment of potential health effects at Camp Lejeune, NRC (2009) concluded that there was "limited/suggestive evidence of an association" between PCE and esophageal, lung, breast, and bladder cancer in humans and that "PCE was reported to cause liver cancer in mice and mononuclear cell leukemia and kidney cancer in rats." Regarding bladder cancer, NRC (2009) identified three epidemiology studies that were not reviewed in IOM (2003): Morgan and Cassady (2002); Blair *et al*. (2003); and Lynge *et al*. (2006). NRC (2009) reported that these studies had inconsistent results, and concluded again that "there is limited/suggestive evidence of an association between chronic exposure to PCE…and bladder cancer." NRC (2009) did not cite any animal or mechanistic studies regarding bladder cancer.

In its 2015 review, an IOM committee reiterated the conclusions of prior NASEM reports. It also identified four additional studies of solvent exposure and bladder cancer that had been published since the NRC (2009) report (Christensen *et al*., 2013; Hansen *et al*., 2013; Lipworth *et al*., 2011; Scott and Jinot, 2011) and stated, "These new studies have generally supported the conclusions of the previous report" (IOM, 2015). IOM (2015) did not cite any animal or mechanistic data regarding PCE and bladder cancer.

7.4.3 US EPA

US EPA (2012) concluded that PCE is "'Likely to be Carcinogenic to Humans' by all routes of exposure," based on "suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the

[12] Matic *et al*. (2014) evaluated bladder cancer risk and glutathione S-transferase gene polymorphisms in a hospital-based case-control study. They reported an interaction between specific polymorphisms and exposure to any solvents, which included PCE, but they did not evaluate risk associated with PCE specifically.

administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence," citing JISA, (1993), NTP (1986b), and NCI (1977) as support for this conclusion. Regarding epidemiology evidence, US EPA (2012) stated that there is "a pattern associating tetrachloroethylene exposure and several types of cancer, including bladder cancer, non-Hodgkin lymphoma and multiple myeloma," and that, "for other sites, including esophageal, kidney, lung, cervical and breast cancer, more limited data suggestive of an effect are available." Regarding animal evidence, US EPA (2012) stated,

> [T]etrachloroethylene increased the incidence of liver tumors (hepatocellular adenomas and carcinomas) in male and female mice and of mononuclear cell leukemia (MCL) in both sexes of rats… Additional tumor findings in rats included significant increases in the NTP bioassay of testicular interstitial cell tumors and kidney tumors in males, and brain gliomas in males and females. In mice, hemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in males in the JISA study.

In this PCE review, US EPA (2012) identified 32 epidemiology studies on PCE exposure and bladder cancer. US EPA (2012) placed the most weight on five studies with exposure methodologies that the agency considered relatively high quality (Calvert *et al*., 2011; Lynge *et al*., 2006; Blair *et al*., 2003; Pesch *et al*., 2000; Aschengrau *et al*., 1993) and four large cohort studies of dry-cleaning workers (Pukkala *et al*., 2009; Wilson *et al*., 2008; Ji *et al*., 2005; Travier *et al*., 2002). In the first set of studies, four of the five reported an increased risk of bladder cancer with PCE exposure; in the second set, the relative risk estimates ranged from 1.01-1.44 (US EPA, 2012). US EPA (2012) concluded that "the pattern of results from this collection of studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude." US EPA (2012) did not present any animal or mechanistic evidence to support this conclusion.

US EPA (2020a) conducted its most recent review of PCE in 2020 and, similar to its 2012 review, concluded "there is a pattern of epidemiological evidence associating PCE exposure with NHL. There is some evidence for bladder cancer and MM but results are mixed. Additional epidemiological data were available showing weaker support for cancers at other sites, including esophageal, lung, and blood (lymphoma). Studies provide more limited support for associations with breast cancer, with little or no support for associations with kidney, esophagus, or liver cancer, and no useful information for cervical cancer." Regarding rodents, US EPA (2020a) concluded there is "conclusive evidence of the carcinogenicity of PCE" for liver cancer, testicular cancer, [mononuclear cell leukemia], renal tubular adenomas and adenocarcinomas, brain gliomas, hemangiosarcomas/hemangiomas, and adenomas of the Harderian gland. Overall, US EPA (2020a) concluded that PCE is considered 'likely to be carcinogenic in humans' by all routes of exposure based on conclusive evidence in animals and suggestive evidence in humans."

US EPA (2020a) identified five additional epidemiology studies of bladder cancer that it considered to "provide little support for an association between bladder cancer and PCE exposure": Bove *et al*. (2014b), Christensen *et al*. (2013), Silver *et al*. (2014), Lipworth *et al*. (2011), and Hadkhale *et al*. (2017). The agency found that these studies showed slight statistically significant increased risks in the medium-exposure groups, but not in the high-exposure groups, and no significant dose-response trend, suggesting that the increases were not PCE-related (US EPA 2020a). US EPA (2020a) concluded, "There is some evidence for [an association between PCE and] bladder cancer…but results are mixed." US EPA (2020a) did not present any animal or mechanistic evidence for PCE and bladder cancer.

7.4.4 IARC

In 2014, IARC did not conclude PCE is a known human carcinogen, but rather "probably carcinogenic to humans (Group 2A)" (IARC, 2014b). Regarding evidence in humans, IARC (2014b) stated, "There is

limited evidence in humans for the carcinogenicity of tetrachloroethylene. Positive associations have been observed for cancer of the bladder." IARC (2014b) further concluded, "Several studies evaluated exposure to tetrachloroethylene and the risk of cancers at other sites, including oesophagus, kidney, cervix, and non-Hodgkin lymphoma. No consistent patterns were seen across studies." Regarding animal evidence, IARC (2014b) concluded, "There is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene" based on evidence related to mononuclear cell leukemia, testicular cancer, kidney cancer, fibroadenomas of the mammary gland, and brain gliomas in rats, and liver cancers, hemangiomas/hemangiosarcomas, and Harderian gland adenomas in mice.

With respect to bladder cancer, IARC (2014b) reviewed five cohort studies (Boice *et al*., 1999; Blair *et al*., 2003; Lynge *et al*., 2006; Calvert *et al*., 2011; Selden and Ahlborg, 2011) and nine case-control studies of PCE and bladder cancer (Aschengrau *et al.*, 1993; Schoenberg *et al*., 1984; Steineck *et al*., 1990; Burns and Swanson, 1991; Swanson and Burns, 1995; Pesch *et al*., 2000; Gaertner *et al*., 2004; Colt *et al*., 2011; Christensen *et al*., 2013) and noted, "While positive associations with bladder cancer were observed in several cohort and case-control studies, and smoking was adequately controlled for in the majority, employment in dry-cleaning was in most cases the only indicator of exposure to tetrachloroethylene, the number of exposed cases was small, and support for an exposure-response relationship was lacking." IARC (2014b) concluded, "The bladder has been identified as a target organ for tetrachloroethylene-induced carcinogenesis in humans; however, there are no mechanistic studies available to support this." IARC (2014b) also did not present any data on bladder cancer from experimental animal carcinogenicity bioassays.

7.4.5 NTP

NTP (2021b) concluded that PCE is "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals." NTP (2021b) stated that PCE caused liver tumors in mice and MNCL in rats, and increased the incidence of benign and malignant kidney tumors in rats. Regarding epidemiology evidence, NTP did not present its own conclusions, but rather stated that the 1995 volume of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans titled "Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals" concluded that there was "limited evidence" for the carcinogenicity of PCE in humans "based mainly on evidence of consistent associations between tetrachloroethylene exposure and esophageal cancer, cervical cancer, and non-Hodgkin lymphoma," but that "confounding by exposure to other chemicals could not be ruled out, and the total numbers in the combined cohort studies were small" (NTP, 2021b). NTP (2021b) did not discuss bladder cancer.

7.4.6 Conclusions

Most government and scientific agencies concluded there is some weak scientific evidence for an association between PCE and bladder cancer, but that the evidence is too limited to address causation (ATSDR, 2019b; IOM, 2003, 2015; US EPA, 2020a; IARC, 2014b; NTP, 2021b). Only two agencies initially concluded there was sufficient evidence for an increased risk in humans (ATSDR, 2017a; US EPA, 2012), but these agencies' conclusions were different in later assessments (ATSDR, 2019b; US EPA, 2020a). ATSDR (2017a) based its conclusion of sufficient evidence on the findings of a slight excess risk in one meta-analysis, one study that reported an increase in bladder cancer among dry-cleaning workers, and one drinking water study. US EPA (2012) based its conclusion of elevated risk in one group of five studies with exposure methodologies that the agency considered relatively high quality, and another group of studies of dry-cleaners with mixed results. In contrast, ATSDR (2019b) concluded the evidence was suggestive but weak, and US EPA (2020a) concluded evidence was mixed. None of the agencies presented any animal or mechanistic evidence regarding PCE and bladder cancer.

7.5 Conclusions

The majority of associations between PCE and bladder cancer in epidemiology studies were statistically null and close to 1. There was no compelling evidence that supports a dose-response relationship, and each study had several methodological limitations that impacted the interpretation of the results (*e.g.*, a high likelihood of exposure misclassification and uncontrolled confounding, particularly by smoking). Animal and MoA evidence does not support causation. In the most recent reviews of the epidemiology evidence, most governmental and scientific agencies concluded there is some weak evidence for a statistical association between PCE and bladder cancer, but that evidence is described as mixed and limited to determine causation (ATSDR, 2019b; IOM, 2003, 2015; US EPA, 2020a; IARC, 2014b; NTP, 2021b). None of the agencies presented any animal or mechanistic evidence regarding PCE and bladder cancer.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans, and (3) there is no MoA with sufficient scientific support, I conclude that, as a whole, scientific evidence does not support a causal association between PCE and bladder cancer.

8 Benzene and Bladder Cancer

In this section, I describe epidemiology and toxicity studies that assessed benzene exposure and bladder cancer, and governmental and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between benzene and bladder cancer.

8.1 Epidemiology

8.1.1 Overview

I identified 44 cohort studies (in 26 unique populations), five case-control studies, one case-cohort study (Shala *et al*., 2023; which I include in the case-control study tables) one pooled analysis of case-control studies and one meta-analysis that evaluated benzene exposure and bladder cancer. Most of these studies were conducted in North America or Europe, but there were also studies in Australia, South Korea, and China. I review here all studies in populations at Camp Lejeune where benzene exposures were specified, even if overlapping, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the most recent study because it had longer follow-up times and/or used more reliable exposure estimates, unless older studies reported additional results (*e.g*., dose-response relationships). I provide an overview, including a brief discussion of cohort and case-control study characteristics, below and in Tables H.1 and H.3. Detailed study quality assessments are described in Table C.1. Study results are discussed in Section 8.1.2 and in Tables H.2, H.4, and H.5. Epidemiology evidence is integrated with experimental evidence in Section 8.3.

8.1.1.1 Study Population

In most cohort studies, exposed and unexposed participants were selected from the same source population. Individuals with and without bladder cancer were also drawn from appropriate populations in most case-control studies. There were two exceptions, Gérin *et al*. (1998) used electoral lists to identify potential controls in a population where voter registration was non-compulsory, and Hadkhale *et al*. (2017) allowed for cases and controls to have a prior history of cancer. Most cohort studies reported high retention rates, but did not always report rates of exclusion, and some of the case-control studies reported low (<80%) participation rates among controls; the latter two aspects increased the potential for selection bias. In all cohort and case-control studies that reported high loss to follow-up or low participation rates, the authors did not report information on how those who were included differed from those who were not, making the assessment of selection bias difficult. As discussed in Section 5, ATSDR (2018a) noted that in its Camp Lejeune study, selection bias could have biased results away from the null.

8.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to benzene *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all studies is the manner by which exposures were estimated. The cohort studies examining benzene exposure and bladder cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, transformer manufacturing workers in Greenland *et al.* [1994]; petroleum or oil refinery workers in Tsai *et al*. [2007]). All studies estimated benzene exposure in an indirect manner, based on job title/history or whether individuals were ever/never exposed to benzene at work, job histories linked to a JEM, or the presence of benzene in drinking water (Camp Lejeune studies). There were no directly measured air or water exposure concentrations evaluated at the individual level in in any studies.

Bove *et al*. (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007b, 2013), along with information on historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). However, neither study had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014b) and ATSDR (2018a), which limits the interpretation of the benzene-specific results.

All case-control studies characterized exposure based on job histories or job histories linked to JEMs. In a few of the studies, job history information was recorded prior to the outcome (*e.g.*, Greenland *et al.,* 1994; Shala *et al*., 2023), but in three studies, self-reported job histories were collected after bladder cancer had been diagnosed (Steineck *et al*., 1990; Gérin *et al*., 1998; Pesch *et al*., 2000). Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between chemical use or exposure and interviews, and potential recall bias where cases may have recalled exposures differently than controls.

Most studies did not consider the frequency, duration, or intensity of potential exposures. The studies that accounted for exposure dose did so based on a JEM, duration of employment, or modeled drinking water contamination (with no individual consumption data); these indirect measurements are often crude and generally do not reflect actual individual exposure levels. In addition, most of the studies did not consider the time-varying nature of potential exposures (*e.g.*, exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

8.1.1.3 Outcome Assessment

Bladder cancer outcomes were obtained or confirmed using reliable and complete methods in most cohort and case-control studies, and all studies had sufficient follow-up time (*i.e.*, ≥5 years). For example, the cohort and case-control studies identified or confirmed cases using medical records, registries, or government databases (*e.g.*, a national death index) except for Greenland *et al*. (1994), where only a subset of the cases identified from employee pension records were medically confirmed. A few studies may have had incomplete ascertainment of cases, namely when relying on self-report to identify cases without another source of identification (such as a registry to identify cases who did not self-report or who were deceased, *e.g.*, ATSDR [2018a]). Most studies reported on bladder cancer incidence or mortality specifically. Eight studies (Satin *et al*., 1996; Lewis *et al*., 2000a; Wong *et al*., 2001a,b; Tsai *et al*., 2003; Huebner *et al*., 2004; Tsai *et al*., 2007; Collins *et al*., 2015) reported cancers of the bladder and other urinary organs combined, and two studies (Steineck *et al*., 1990; Pesch *et al*., 2000) reported on urothelial cancers, which did not provide an accurate estimate of the benzene/bladder cancer-specific association.

8.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. All studies controlled for age and sex (except Pukkala, 1998, which did not appear to control for sex), but other variables were controlled for less consistently (*e.g.*, smoking). None of the studies considered or controlled for prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics. Even when important covariate data were collected, none of the studies accounted for the time-varying nature of certain covariates in analyses (*e.g.*, smoking). Most of the studies did not provide information on the degree or impact of missing covariate data.

8.1.1.5 Temporality

Most of the cohort studies considered or assessed exposures occurring prior to the outcome, but many did not ensure an adequate period of time between exposure and diagnosis, either in the design or the analysis (*e.g.*, incorporating a lag) to account for a latency period (*i.e.*, ≥4 years for bladder cancer [CDC, 2015]). Many studies appeared to include cases in the analysis that could have occurred <4 years after the exposure, undermining the ability to properly assess an exposure-outcome relationship, although in most instances, there was a long enough duration of follow-up that this is likely not a large concern. Of the case-control studies, three studies (Steineck *et al.*, 1990; Hadkhale *et al.*, 2017; Shala *et al.*, 2023) appropriately considered the latency period.

8.1.2 Study Results

Cohort and case-control studies reported a wide range of risk estimates for benzene and bladder cancer. Of studies that reported any cases of bladder cancer risk estimates for incidence and mortality ranged from 0.2-3.0 and 0.0-12.5, respectively, but almost all were statistically null and around 1 (both above and below). Three cohort studies (Satin *et al.*, 1996; Bulbulyan *et al.*, 1999; Wong *et al.*, 2001b) and three case-control studies (Gérin *et al.*, 1998; Hadkhale *et al.*, 2017; Shala *et al.*, 2023) reported statistically significant results.

Bulbulyan *et al.* (1999), in their study of printing plant employees in Russia, found that press operators had a statistically significantly increased risk of bladder cancer mortality (SMR = 12.5, 95% CI: 1.5-45.1). This is by far the largest risk of bladder cancer mortality observed in any study, but this result was based on only two deaths. In addition, benzene use in bookbinding was discontinued 22 years prior to follow-up and expected deaths were based only on a single rate reported in 1992. In contrast, Wong *et al.* (2001b) observed a statistically significant *decreased* bladder and other urinary organ cancer mortality risk among oil refinery employees (SMR = 0.592, 95% CI: 0.324-0.993), as well as male maintenance workers only (SMR = 0.328). Satin *et al.* (1996) observed a statistically significant decrease in bladder and other urinary organ cancer mortality among oil refinery workers when compared with the US general population (SMR = 0.559, 95% CI: 0.362-0.825). In analyses stratified by sex, length of employment, years since hired, and period of hire, SMRs were generally below 1 (particularly for men, long durations of employment and years since hired, and all periods of hire) but were not statistically significant. It is also notable that many other cohort studies reported 0 exposed cases and risk estimates of 0 for various stratified results (*e.g.*, Dagg *et al.*, 1992; Koh *et al.*, 2011).

In a nested case-control study that relied on the Nordic Occupational Cancer database, which included 113,343 bladder cancer cases across four countries, Hadkhale *et al.* (2017) found a statistically significant increased risk of bladder cancer incidence among individuals with a cumulative benzene exposure of 15.04 ppm or greater (HR = 1.16, 95% CI: 1.04-1.31), as well as among individuals under 50 years of age with a

cumulative benzene exposure of 15.04 ppm or greater (HR = 1.22, 95% CI: 1.03-1.44). However, these associations were based on self-reported occupational history from decennial censuses and a JEM. Shala *et al*. (2023) reported an elevated risk of bladder cancer incidence among benzene-exposed offshore petroleum workers with 18.8 to 33.5 years of exposure when compared to unexposed workers (HR = 1.89, 95% CI: 1.14-3.13); there was also a significant trend based on exposure duration (p_{trend} = 0.044). These results should be interpreted with caution, however, as 31% of eligible controls did not participate and these results were based on indirect exposure assessments (*i.e*., from work history information, job codes, and a JEM). Finally, in a Canadian case-control study, Gérin *et al*. (1998) observed a statistically significant decreased risk of bladder cancer incidence when compared with unexposed individuals (OR = 0.2, 95% CI: 0.0-0.6), although this was based on only 2 cases. Two case-control studies investigated the risk of urothelial cancer among subjects exposed to benzene (Steineck *et al*., 1990; Pesch *et al*., 2000) and neither study observed any differences in risk between exposed and unexposed subjects.

I identified one pooled study that estimated the association between benzene and bladder cancer (Table H.5). Sciannameno *et al*. (2018) linked occupational data from two case-control studies to a JEM to estimate the probability and intensity of benzene exposures. Most reported risk estimates were close to 1 (range: 0.94-1.08) and none were statistically significant. The two case-control studies used in the pooled analysis did not report any information on benzene, so they are not reviewed here. Regardless, because the pooled analysis relied on an indirect exposure assessment (*i.e*., occupational data linked to a JEM), the pooled analysis is limited by the potential for exposure misclassification. Seyyedsalehi *et al*. (2024) conducted a meta-analysis of 35 cohort and case-control studies examining benzene exposure and risk of bladder cancer incidence or mortality. The analysis found an increased risk of incident bladder cancer based on 17 cohort and case-control studies (RR = 1.10, 95% CI: 1.01-1.20). There were no associations reported in analyses stratified by geographic region, quality score, control for tobacco smoking, exposure circumstance, or sex. However, when stratified by year of publication, there was an increased risk of bladder cancer incidence and mortality combined (RR = 1.11, 95% CI: 1.01-1.21) in studies published in 2000 or later. There were no associations reported for any level of exposure in analyses stratified by level or dose of benzene exposure.

8.1.3 Conclusions

Most cohort and case-control studies did not report associations between benzene exposure and bladder cancer or demonstrate exposure-response relationships. All studies had critical methodological limitations that impact the interpretation of their results, particularly with respect to exposure measurements, and most studies did not account for all relevant confounders (*e.g*., smoking). I conclude that the epidemiology evidence does not support a causal association between benzene exposure and bladder cancer.[13]

8.2 Toxicology

8.2.1 Animal Carcinogenicity Studies

I identified seven chronic oral bioassays and one chronic inhalation bioassay of benzene that evaluated the bladder. The results of these studies are reported in Attachment I, Tables I.1 and I.2. An overview of study quality is described in Attachment I, Table I.3, and the quality of individual chronic studies is shown in Attachment I, Table I.4. Experimental evidence is integrated with epidemiology evidence in Section 8.3.

[13] The results of the study by Xie *et al*. (2024), which I identified after the completion of my literature search (Section 6.1.2), do not change my conclusions regarding TCE exposure and bladder cancer risk.

Overall, the chronic bioassays had several methodological limitations, and none reported any bladder tumor data for rats or mice of either sex. These studies do not provide evidence that benzene can cause bladder cancer.

8.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which benzene could cause bladder cancer. In animals and humans, benzene is primarily metabolized in the liver, and secondarily in the bone marrow, to reactive metabolites that are electrophilic, pro-oxidant, genotoxic, and immunosuppressive (IARC, 2018; ATSDR, 2007a, 2024; US EPA, 1998). The toxicity of benzene is dependent on the formation of these reactive metabolites, with evidence suggesting that they may induce certain leukemia subtypes (AML and MDS) *via* a genotoxic MoA. Although the precise mechanisms have not been fully elucidated, various processes are believed to be involved, including oxidative stress, protein and DNA damage, disruption of gene expression, genomic instability, decreased DNA repair, enzyme inhibition, immune dysfunction, inflammation, chromosome damage, epigenetic changes, and altered cell functions, including proliferation, cell death, and receptor-mediated effects (IARC, 2018; ATSDR, 2007a, 2024; US EPA, 1998; North *et al*., 2020). Reactive metabolites generated in the liver can also be transported to the bone marrow (ATSDR, 2024).

Cytogenetic abnormalities, including chromosomal aberrations (hypo- and hyperdiploidy, deletions, breaks, and gaps) in peripheral lymphocytes and bone marrow cells are commonly observed in benzene-exposed humans (ATDSR, 2007a). Although benzene is considered genotoxic, mechanistic evidence suggests it is not a direct-acting DNA mutagen, but rather indirectly induces genotoxicity through a threshold-mediated process in which exposures below the threshold do not result in genetic toxicity (North *et al*., 2020). Evidence from epidemiology studies also provides support for a threshold below which benzene does not cause cancer (Rhomberg *et al*., 2016).

Metabolic activation in the liver and bone marrow, followed by various downstream effects resulting in genotoxicity, is generally accepted as a biologically plausible MoA for the association between benzene and certain leukemia subtypes, but whether this MoA is applicable to other types of cancers that are etiologically distinct, including bladder cancer, is unknown.

8.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated benzene and bladder cancer (see Sections 8.1 and 8.2). Most of these epidemiology studies had higher-quality study designs and outcome assessments and had low likelihoods of selection bias. Appropriate consideration of temporality, latency period, and control for potential confounders varied across studies, but none sufficiently controlled for all important potential confounders, particularly smoking. Most importantly, although some studies used semi-quantitative exposure estimates, none of the epidemiology studies adequately assessed benzene exposures, calling into question the validity of reported risk estimates. In addition to being limited in number and quality, animal studies do not provide evidence for causation. Keeping study strengths and weaknesses in mind, I review the available evidence as a whole in the context of Bradford Hill's considerations in Table 8.1. I conclude that the evidence does not support a causal association between benzene and bladder cancer.

Table 8.1 Bradford Hill Assessment of Benzene and Bladder Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between benzene exposure and bladder cancer in cohort and case-control studies.
Consistency	Most studies reported weak risk estimates that were close to 1 and statistically null.
Specificity	The evidence does not support a specific relationship between benzene and bladder cancer.
Temporality	Temporality was adequately addressed in a few cohort and case-control studies, but rarely was an appropriate latency period considered.
Dose-Response	There were no consistent trends of increasing risk with increasing exposures across the studies that considered multiple exposure levels.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which benzene could cause bladder cancer.
Coherence	Collectively, the evidence does not support a causal association between benzene exposure and bladder cancer. The majority of the associations between benzene and bladder cancer in epidemiology studies were statistically null and close to one, there were no consistent dose-response relationships across studies, and several epidemiology studies had methodological limitations that impacted the interpretation of results. Although there is evidence that reactive metabolites of benzene may cause cancer *via* a mutagenic MoA, or through alterations in cell proliferation, cell death, or receptor-mediated effects (IARC, 2018; ATSDR, 2007a; US EPA, 1998), there is no evidence that benzene causes bladder cancer in animal models.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to benzene that cause bladder cancer.

Note:
MoA = Mode of Action.

8.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.7). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Overall, governmental and international agencies did not conclude there was evidence for an association between benzene and bladder cancer. Agency assessments of benzene carcinogenicity are described below.

8.4.1 ATSDR

In its 2007 "Toxicological Profile for Benzene," ATSDR concluded that benzene can cause leukemia, and stated that there was "suggestive evidence of associations" between occupational exposure to benzene and NHL (ATSDR, 2007a). The agency discussed two studies that did not find bladder tumors, and in its 2015 Supplemental Report (ATSDR, 2015), bladder cancer was not discussed. In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "below equipoise evidence for causation" for benzene and bladder cancer due to insufficient information. ATSDR (2017a) did not discuss any animal data. In 2024, ATSDR released a Draft Toxicological Profile for Benzene for Public Comment. Bladder cancer is not discussed in this report (ATSDR, 2024b).

8.4.2 NASEM

IOM (2003) concluded that there was "inadequate/insufficient evidence" to determine whether there was an association between benzene and bladder cancer. IOM (2003) identified two studies that included data on benzene exposure based on job histories that showed either no association (Gerin *et al*., 1998) or mixed results that depended on the methods of exposure estimation (Pesch *et al*., 2000). The agency did not cite any animal or mechanistic data. NRC (2009) stated that NHL and multiple myeloma have been associated with occupational exposure to benzene, but that "these associations have not been consistently observed across studies." NRC (2009) and IOM (2015) did not discuss benzene and bladder cancer.

8.4.3 US EPA

US EPA (1998) classified benzene as a known human carcinogen based primarily on increased risks of acute myeloid leukemia (AML) in epidemiology studies. US EPA did not discuss bladder cancer in its review of the carcinogenic effects of benzene (US EPA, 1998).

8.4.4 IARC

IARC (2012b) concluded, "There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia." IARC (2012b) did not discuss bladder cancer.

IARC (2018) concluded, "There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia in adults." IARC (2018) also noted that "[t]here is sufficient evidence in experimental animals for the carcinogenicity of benzene" and the "Group 1 evaluation was supported by mechanistic data." The agency identified six occupational studies of benzene exposure and bladder cancer (Linet *et al*., 2015; Koh *et al*., 2011; Greenland *et al*., 1994; Wong, 1987; Sorahan *et al*., 2005; Bulbulyan *et al*., 1999), but did not draw any conclusions regarding an association and did not cite any animal or mechanistic data regarding bladder cancer.

8.4.5 NTP

NTP (2021c) concluded "benzene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans." NTP (2021c) indicated that the strongest evidence was from

occupational cohort studies that found associations with leukemia – "mainly acute myelogenous leukemia." NTP (2021c) noted that case-control studies were "limited by poorly defined exposures and mixed exposure patterns." NTP (2021c) did not discuss any bladder cancer epidemiology studies.

NTP (2021c) further stated that "benzene causes cancer at numerous tissue sites in rodents." NTP (2021c) indicated that this includes malignant lymphoma in mice of both sexes after oral exposures in the Huff *et al*. (1989)/NTP (1986a) study and "a tendency towards induction of lymphoid tumors in mice," citing subchronic studies (IARC, 1982, 1987). NTP (2021c) did not discuss bladder tumors.

8.4.6 Conclusions

Overall, governmental and international agencies did not conclude there was evidence for an association between benzene and bladder cancer.

8.5 Conclusions

Government and international agencies have either not reviewed the evidence (ATSDR, 2007a, 2015; NRC, 2009; IOM, 2015; US EPA, 1998), have not drawn conclusions (IARC, 2018), or have concluded that there is inadequate or insufficient evidence to evaluate an association between benzene and bladder cancer in humans (ATSDR, 2017a; IOM, 2003). There is no evidence that benzene causes bladder cancer in animal models, and epidemiology evidence does not support a causal association. Most epidemiology studies reported risk estimates around 1, and statistically significantly increased associations were only reported in a few studies with indirect or non-specific exposure measurements. In addition, the epidemiology evidence is based on studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans, and (3) there is no MoA with sufficient scientific support, I conclude, as a whole, the evidence does not support a causal association between benzene and bladder cancer.

9 Vinyl Chloride and Bladder Cancer

In this section, I describe epidemiology and toxicity studies that assessed vinyl chloride exposure and bladder cancer, and governmental and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between vinyl chloride and bladder cancer.

9.1 Epidemiology

9.1.1 Overview

I identified seven cohort studies (in five unique populations) that evaluated vinyl chloride exposure and bladder cancer; I did not identify any case-control studies, pooled analyses or meta-analyses. All of these were conducted in the US. I review here all studies in populations at Camp Lejeune where vinyl chloride exposures were specified, even if overlapping, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the most recent study because it had longer follow-up times and/or used more reliable exposure estimates, unless older studies reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of study characteristics and quality, below, and this is reviewed in more detail in Tables C.1. and J.1. Study results are discussed briefly in Section 9.1.2 and reviewed in more detail in Table J.2. Epidemiology evidence is integrated with experimental evidence in Section 9.3.

9.1.1.1 Study Population

Two studies evaluated vinyl chloride exposure and bladder cancer in populations living or working at Camp Lejeune (Bove *et al*., 2014b; ATSDR, 2018a), and three studies examined the relationship in chemical or plastics workers (Teta *et al*., 1990; Carreón *et al*., 2014; Mundt *et al*., 2017). All studies had appropriate study and comparison groups, though Teta *et al*. (1990) compared subjects of varying races/ethnicities to a white population. Most studies had high participant retention; however, Teta *et al*. (1990) and Bove *et al*. (2014b) did not report whether any participants were excluded from their analysis, and ATSDR (2018a) reported low participation rates. As discussed in Section 5, ATSDR (2018a) noted that in its Camp Lejeune study, selection bias could have biased results away from the null.

9.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to vinyl chloride *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all studies is how exposures were estimated. The cohort studies examining vinyl chloride exposure and bladder cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, chemical or plastics workers). All studies estimated vinyl chloride exposure in an indirect manner, based on job title/history, whether individuals were ever or never exposed to vinyl chloride at work, or the presence of vinyl chloride in drinking water (Camp Lejeune studies). Bove *et al*. (2014b) and ATSDR (2018a) estimated individual exposures at Camp Lejeune using modeled average

monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007b, 2013) along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). However, neither study had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014b) and ATSDR (2018a), which limits the interpretation of the vinyl chloride-specific results. Carreón *et al*. (2014) was the only other study that considered duration of exposure (based on duration of employment); other occupational studies did not consider intensity or frequency of exposure.

9.1.1.3 Outcome Assessment

One study examined bladder cancer incidence (ATSDR, 2018a) and the other four examined bladder cancer mortality. Because bladder cancer is not always fatal, analyses evaluating incidence are more informative than those evaluating mortality. All studies had sufficient follow-up time for cancer to develop (range: 10-72 years).

For all but one study (ATSDR, 2018a), data on bladder cancer outcomes were obtained or confirmed using reliable methods based on identification or confirmation in medical records, registries, or government databases (*e.g*., national death index), resulting in complete or near complete ascertainment of cases. ATSDR (2018a) may have incompletely ascertained cases, as it relied on self-report to identify cases without another source of identification, such as a registry, to identify cases who did not self-report or who had died.

Finally, the Camp Lejeune studies and Teta *et al*. (1990) examined bladder cancer specifically, while Mundt *et al*. (2017) and Carreón *et al*. (2014) examined cancers of the bladder and other urinary organs combined, which did not provide an accurate estimate of the vinyl chloride/bladder cancer specific association.

9.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. All studies controlled for age and sex, but other variables were controlled for less consistently (*e.g*., race or ethnicity). None of the studies considered or controlled for prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics.

None of the studies controlled for smoking. One Camp Lejeune study (Bove *et al*., 2014b) attempted to quantify the bias due to smoking through various means of examining the risk of cancers that are associated with smoking but not with solvents. Bove *et al*. (2014b) reported no associations in these analyses, suggesting that smoking is not a confounder in other analyses of smoking-related cancers. There is no evidence, however, that the lack of associations in analyses of the smoking-related cancers or the adjustments of risk estimates for any observed associations adequately addressed confounding by smoking.

Reporting on the degree or potential impact of missing covariate data varied. Even when important covariate data were collected, none of the studies accounted for the time-varying nature of certain covariates in analyses (*e.g*., smoking).

9.1.1.5 Temporality

All studies had documented exposures prior to the onset of disease, but the exposure and follow-up periods overlapped in ATSDR (2018a) and the authors were not clear with respect to how that was handled in the analysis. Bove *et al*. (2014b) appropriately incorporated 10-year lags into some of their analyses, and ATSDR (2018a) reported that "virtually all" participants developed cancer ≥10 yrs after being stationed or employed at CL. No other study considered disease latency in its analyses, although in most instances, there was a long enough duration of follow-up that this is likely not a large concern.

9.1.2 Study Results

Almost all reported risk estimates for bladder cancer overall and for bladder and other urinary organ cancer were close to 1 and not statistically significant, ranging from 0.00-2.59. No study reported statistically significant risks.

Two studies examined at least three levels of exposure (*i.e*., based on dose, duration, or frequency). Only Bove *et al*. (2014b) examined risks associated with vinyl chloride-specific exposures. The categorical vinyl chloride exposures used in ATSDR (2018a) were reported to be completely correlated with TCE, benzene, and total VOCs ($\gamma = 0.99$). In Bove *et al*. (2014b) and ATSDR (2018a), there were no clear trends of either increasing or decreasing risk with increasing exposure (*i.e*., risk estimates across exposure categories were either flat or non-linear).

9.1.3 Conclusions

No study reported associations between vinyl chloride exposure and bladder cancer or demonstrated clear exposure-response relationships. All studies had critical methodological limitations, including that only one assessed vinyl chloride-specific exposures, and that study did not link the modeled exposures in drinking water to individual water consumption data. All studies likely had residual and uncontrolled confounding. The high likelihood of exposure misclassification and confounding likely resulted in inaccurate and biased risk estimates that are difficult to interpret. I conclude that the epidemiology evidence does not support a causal association between vinyl chloride exposure and bladder cancer.

9.2 Toxicology

9.2.1 Animal Carcinogenicity Studies

I identified three oral, one intraperitoneal, and nine inhalation chronic bioassays, as well as five inhalation subchronic bioassays, that stated they evaluated vinyl chloride exposure and the bladder. The results of the chronic studies are reported in Attachment K, Tables K.1-K.3; an overview of chronic study quality is described in Attachment K, Table K.4, and the quality of individual chronic studies is shown in Attachment K, Table K.5. Experimental evidence is integrated with epidemiology evidence in Section 9.3.

The three chronic oral vinyl chloride bioassays that stated they examined the bladder do not provide evidence that vinyl chloride is associated with bladder tumors. Feron *et al*. (1981) reported a single unclassified epithelial cell tumor in a male rat dosed with 5.0 mg/kg-d of vinyl chloride, but the authors did not specify whether this tumor was benign or malignant, and it was not considered to be treatment-related. No additional bladder tumors were reported in male or female Wistar rats dosed with up to 14.1 mg/kg-day of vinyl chloride *via* diet or 300 mg/kg-day vinyl chloride *via* gavage, although the exposure duration was

inappropriate, as it was based on the point at which 75% of the control rats spontaneously died. Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) reported a single bladder carcinoma in one male control rat, and a single bladder papilloma in one male rat gavaged with 5 mg/kg-d of vinyl chloride for 52 weeks; no additional bladder tumors were reported at gavage doses up to 50 mg/kg-d. Of the nine inhalation chronic bioassays that stated that they evaluated the bladder, none reported bladder tumors, although they all exposed animals for ≤76 weeks.

Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) described a chronic intraperitoneal injection vinyl chloride bioassay, and reported a single bladder tumor in a female rat injected with 4.25 mg vinyl chloride twice at 2-month intervals, and a single bladder tumor in a male rat injected with 4.25 mg vinyl chloride four times at 2-month intervals, but these tumors were not treatment-related.

Overall, animal evidence does not support vinyl chloride as a cause of bladder cancer in humans. Treatment-related bladder tumors were not reported in any chronic vinyl chloride bioassay, though all were of low study quality.

9.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which vinyl chloride could cause bladder cancer. In animals and humans, vinyl chloride is metabolized in the liver to reactive intermediates, including a highly reactive, short-lived epoxide intermediate (2-chloroethylene oxide) that can directly bind to DNA and cause base-pair transitions (*e.g*., G→A and A→T), ultimately resulting in the potential development of liver angiosarcoma, an extremely rare type of liver cancer in humans (ATSDR, 2024a; US EPA, 2000; IARC, 2012a).

Although this genotoxic MoA resulting from metabolic activation is well characterized for the development of liver angiosarcoma, it has not been demonstrated for etiologically distinct cancers in other organs and tissues, including bladder cancer. Because the primary mechanism involves the direct interaction of the intermediate with DNA in the liver, this MoA is likely specific to the liver where the reactive intermediate is formed. Owing to the high reactivity and short-lived nature of the 2-chloroethylene oxide intermediate, migration to other tissues, including the bladder, is unlikely to occur (US EPA, 2000). Overall, there is no consistent or compelling evidence to support a biologically plausible mechanism by which vinyl chloride could cause bladder cancer.

9.3 Evidence Integration

A small number of epidemiology and toxicity studies have evaluated vinyl chloride exposure and bladder cancer (see Sections 9.1 and 9.2). All epidemiology studies had higher-quality study designs (*i.e*., cohort) and outcome assessments. Appropriate consideration of latency period and control for potential confounders varied across studies, but none sufficiently controlled for all important potential confounders, particularly smoking. Most importantly, none of the epidemiology studies adequately assessed vinyl chloride exposures, calling into question the validity of reported risk estimates. Although limited in number and quality, animal studies do not provide evidence for causation. Keeping study strengths and weaknesses in mind, I review the available evidence as a whole in the context of Bradford Hill's considerations in Table 9.1. I conclude that the evidence does not support a causal association between vinyl chloride and bladder cancer.

Table 9.1 Bradford Hill Assessment of Vinyl Chloride and Bladder Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between vinyl chloride exposure and bladder cancer in epidemiology studies.
Consistency	Most studies reported risk estimates close to 1 and all were statistically null.
Specificity	The evidence does not support a specific relationship between vinyl chloride and bladder cancer.
Temporality	Temporality was adequately addressed in all epidemiology studies, but not all studies appropriately considered a latency period.
Dose-Response	There is no evidence of a dose-response relationship between vinyl chloride exposure and bladder cancer.
Biological Plausibility	The evidence does not support a biologically plausible mechanism by which vinyl chloride can cause bladder cancer.
Coherence	Collectively, the evidence does not support a causal association between vinyl chloride exposure and bladder cancer. The majority of the associations between vinyl chloride and bladder cancer in epidemiology studies were statistically null and close to 1, there were no dose-response trends reported, and each study had several methodological limitations that impacted the interpretation of results. While there is a biologically plausible MoA by which vinyl chloride can cause liver cancer, there is no evidence for a plausible MoA for bladder cancer, and vinyl chloride did not cause bladder cancer in animal bioassays.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compound to vinyl chloride that causes bladder cancer.

Note:
MoA = Mode of Action.

9.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.7). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Bladder cancer was not discussed in vinyl chloride assessments by ATSDR (2006, 2016, 2023), IARC (2012a), NRC (2009), IOM (2003, 2015), or US EPA (2000a). ATSDR (2017a) concluded there was

"below equipoise evidence for causation." These agency assessments of vinyl chloride carcinogenicity are described below.

9.4.1 ATSDR

In its 2006 "Toxicological Profile for Vinyl Chloride," ATSDR concluded that the strongest human evidence with respect to cancer comes from "the cluster of reports of greater than expected incidences of liver angiosarcoma" and said that liver angiosarcoma had been observed in several animal species. ATSDR (2006) noted that cancer has also been observed in other tissues (*i.e.*, respiratory tract, lymphatic/hematopoietic system, and the brain and central nervous system), but discussed uncertainties with these associations. ATSDR (2006) did not make a determination regarding bladder cancer, nor did it discuss any epidemiology studies or bladder tumors in animal bioassays. In the subsequent "Addendum to the Toxicological Profile for Vinyl Chloride," ATSDR (2016) did not make additional conclusions regarding cancer.

In its most recent Toxicological Profile for Vinyl Chloride, ATSDR (2024a) maintained the conclusions of its 2006 evaluation, concluding that the strongest human evidence with respect to cancer is for liver angiosarcoma, which is a rare tumor type, with sufficient evidence from experimental animal studies. While ATSDR (2024a) noted that tumors have also been observed in the mammary gland, lung, and adipose tissue, the agency concluded there is little consistency in the findings across species. Similar to the 2006 evaluation, ATSDR (2024a) did not make a determination regarding bladder tumors, nor did it discuss any epidemiology studies or bladder tumors in animal bioassays. The agency noted that the carcinogenicity of vinyl chloride likely is a result of the formation of reactive metabolites followed by direct interaction with DNA, but this mechanism was not discussed in the context of bladder cancer.

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "below equipoise evidence for causation" for bladder cancer due to insufficient information. ATSDR (2017a) did not discuss evidence regarding bladder cancer in any animal or mechanistic studies.

9.4.2 NASEM

In its 2003 review, an IOM committee did not discuss animal or mechanistic data or make any conclusions regarding bladder cancer (IOM, 2003). NRC (2009) stated that "there is limited/suggestive evidence of an association between chronic exposure to…mixtures of organic solvents and bladder cancer," but did not discuss any epidemiology, animal, or mechanistic studies regarding vinyl chloride specifically and bladder cancer. IOM (2015) did not include any discussion of bladder cancer and vinyl chloride specifically.

9.4.3 US EPA

US EPA (2000a) concluded that vinyl chloride is a known human carcinogen by the inhalation and oral routes of exposure, and highly likely to be carcinogenic by the dermal route, based on sufficient evidence for liver angiosarcoma and hepatocellular carcinoma in humans, consistent evidence of liver carcinogenicity in experimental animals, and supportive mechanistic evidence. US EPA (2000a) did not discuss any epidemiology, animal, or mechanistic evidence regarding and bladder cancer.

9.4.4 IARC

IARC (2008) classified vinyl chloride as a Group 1 carcinogen. The agency concluded, "There is sufficient evidence in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcoma of the liver, and hepatocellular carcinoma." IARC (2008) also noted that "[t]here is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride." IARC (2008) did not discuss any epidemiology, animal, or mechanistic evidence regarding bladder cancer.

In an updated evaluation, IARC (2012a) maintained the same conclusions, discussing sufficient evidence for carcinogenicity of vinyl chloride based on angiosarcoma of the liver and hepatocellular carcinoma in humans and sufficient evidence from experimental animal studies. IARC (2012a) did not discuss any epidemiology, animal, or mechanistic evidence regarding bladder cancer.

9.4.5 NTP

NTP (2021d) concluded that "vinyl chloride is known to be a human carcinogen based on sufficient evidence from carcinogenicity studies in humans." NTP (2021d) noted that the strongest evidence was from epidemiology studies and case reports showing associations with hepatic angiosarcoma, a rare tumor type in humans.

NTP (2021d) further stated that "vinyl chloride caused tumors in three rodent species, at several different tissue sites, and by several different routes of exposure." The agency also noted that the carcinogenicity of vinyl chloride is likely attributable to metabolism of vinyl chloride to chloroethylene oxide and chloroacetaldehyde, both of which can form etheno DNA adducts. The etheno adducts can cause base pair substitutions, and to a lesser degree, frameshift mutations. NTP (2021d) did not discuss any epidemiology, animal, or mechanistic evidence with respect to bladder cancer.

9.4.6 Conclusions

Bladder cancer was not discussed in vinyl chloride assessments by ATSDR (2006, 2016, 2023), IARC (2012a), NRC (2009), IOM (2003, 2015), or US EPA (2000a). ATSDR (2017a) concluded there was "below equipoise evidence for causation."

9.5 Conclusions

Most government and international agencies did not discuss bladder cancer in their reviews of vinyl chloride (ATSDR, 2006, 2016, 2024a; IARC, 2012a; NRC, 2009; IOM, 2003, 2015; US EPA, 2000a). ATSDR (2017a) concluded there was "below equipoise evidence for causation" for bladder cancer due to insufficient information. Although these studies had methodological limitations, treatment-related bladder tumors were not reported in any chronic vinyl chloride bioassays. The epidemiology evidence does not support an association between vinyl chloride and bladder cancer, as most epidemiology studies reported risk estimates that were close to 1 and no study reported statistically significant associations. All epidemiology studies had a high likelihood of exposure misclassification and uncontrolled confounding, particularly for smoking. Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans and (3) there is no MoA with sufficient scientific support, I conclude, as a whole, the evidence does not support a causal association between vinyl chloride and bladder cancer.

10 *trans*-1,2-DCE and Bladder Cancer

In this section, I discuss studies that assessed *trans*-1,2-DCE exposure and bladder cancer, and a government agency review of this evidence. I conclude that scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE exposure and bladder cancer.

I did not identify any epidemiology studies that investigated *trans*-1,2-DCE exposure and the risk of bladder cancer. I identified several studies of Marines and Navy personnel or civilian employees at Camp Lejeune that investigated risks associated with being stationed at or working on base, or with estimated exposures to total volatile organic compounds (TVOC) combined on base, but none specifically evaluated risks associated with *trans*-1,2-DCE (see Section 5). As such, they do not provide information with respect to *trans*-1,2-DCE.

I did not identify any chronic *trans*-1,2-DCE animal toxicity studies. NTP (2002) exposed F344/N rats and B6C3F1 mice to *trans*-1,2-DCE in feed for 14 weeks at doses ranging from 3,125 to 50,000 parts per million (ppm). NTP (2002) did not identify any tumors in rats or mice. In other studies cited by NTP, *trans*-1,2-DCE was determined not to be genotoxic when evaluated by *in vitro* and *in vivo* methods (Greim *et al*., 1975; Sawada *et al*., 1987; Mortelmans *et al*., 1986; Černá and Kypěnová, 1977; all as cited in NTP, 2002), and NTP (2002) stated, "No information was found in a search of the literature regarding the carcinogenicity of *cis*-, *trans*-, or *cis,trans*-1,2-dichloroethylene in animals or humans."

To my knowledge, ATSDR's draft "Toxicological Profile for 1,2-Dichloroethene" is the only agency review of *trans*-1,2-DCE. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to *trans*-1,2-dichloroethene…were located."

The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and bladder cancer.

11 Mixtures

People are typically exposed to complex mixtures of chemicals from various sources, including food, drinking water, air, and consumer products, on a daily basis (Feron and Groten, 2002). While people are not adversely affected by these near-constant exposures to chemical mixtures in the environment, in some cases, simultaneous exposures to several chemicals at sufficient concentrations may result in chemical interactions that alter the toxicity of the individual chemicals. The nature of these interactions depends on the specific chemicals, their concentrations, their respective MoAs (*i.e.*, the type of mechanism that can lead to toxicity in the body), and the frequency, duration, and route of exposure to each (ATSDR, 2004).

In general, chemicals' joint toxic actions may be either additive (the toxic effects produced by exposure to several chemicals at once is equal to the sum of their individual effects), synergistic (the toxic effects produced by exposure to several chemicals is equal to greater than the sum of their individual effects because interactions enhance the toxicity of each chemical), or antagonistic (the toxic effects produced by exposure to several chemicals is equal to less than the sum of their individual effects because interactions diminish the toxicity of each chemical) (ATSDR, 2004). Chemicals' joint toxic actions at relatively low exposure concentrations, such as those encountered in the ambient environment, usually result in effects that are additive or less than additive (Cassee *et al*., 1998; Borgert *et al*., 2004). For additive joint toxic actions to occur, the chemicals in a mixture must act independently and not amplify each other's toxicity.

To determine whether the components of a chemical mixture are additive, one must evaluate each individual component's MoA, movement throughout the body (called pharmacokinetics), and toxicity in specific tissues of the body (US EPA, 2007). In the absence of information regarding potential interactions, US EPA guidance for chemical mixture risk assessment assumes additive joint toxic actions for constituents of a mixture that have the same or a similar MoA and/or tissue where they can exert effects (US EPA, 1989, 2000, 2007). This is a conservative approach, because assuming additivity can result in an overestimate of the risk of health effects for the chemical mixture (Cassee *et al*., 1998).

Regarding the potential for additive effects, Bloch *et al*. (2023) explained, "The probability of additive effects of substances in a mixture will decrease with the number of different molecular targets they act upon and with the number of different cell types and tissues that are affected due to differences in toxicokinetics." Similarly, regarding the potential for synergistic effects, Kortenkamp *et al*. (2009) stated, "Deviations from predicted additivity, indicative of synergisms or antagonisms, are comparatively rare, relatively small and largely confined to mixtures with only a few compounds. Any synergistic interaction between the mixture components can be expected to be highly scenario specific, depending on the number and nature of the involved components, the exposed organisms and analyzed endpoint."

The exposure concentrations of each component in a mixture are also the key drivers for potential synergistic effects. The available literature suggests that there is little to no likelihood of synergistic interactions between chemicals present in a mixture at low concentrations (*i.e.*, at or below their individual toxicity thresholds) typical of environmental exposures (Charles *et al*., 2007; Crofton *et al*., 2005; Feron *et al*., 1995). Cedergreen (2014) reviewed the scientific literature on potential interactions among environmental chemical exposures to evaluate whether any groups of substances tend to elicit synergistic interactions and concluded that "true synergistic interactions between chemicals are rare and often occur at high concentrations."

Without a direct evaluation of the chemicals and their concentrations in a particular mixture, it is not possible to know for certain if chemical interactions will occur, and to what extent. Because of this, as well as the general understanding that synergistic interactions are rare and do not typically occur at low levels of exposure, there is no evidence to indicate that there would be additive or synergistic effects on toxicity from exposure to a mixture of the chemicals of concern simply because they are present in the ambient air or water as a chemical mixture.

Finally, while combined exposures to multiple chemicals may be additive or synergistic in experimental animals, this does not provide any indication of whether combined effects would occur in animals of other species, in animals of other strains of the same species, or in subjects of different ages (Mauderly and Samet, 2009). Interspecies, interstrain, and age-related differences exist in susceptibility and sensitivity to adverse effects. It is also possible that synergisms occurring at an intermediate step in an MoA may not manifest at clinical and public health scales in human populations (Mauderly and Samet, 2009).

Scientific evidence does not demonstrate TCE, PCE, benzene, vinyl chloride, or *trans*-1,2-DCE can cause bladder cancer (discussed in Sections 6-10). Each of these chemicals has a distinct MoA, targeting different cell types and operating through separate molecular pathways. Thus, evidence does not support the hypothesis that exposure to a mixture of these chemicals could act in an additive or synergistic manner with respect to bladder cancer causation.

12 Conclusions

Across the five studies that evaluated bladder cancer risks among Marines or Navy personnel stationed at Camp Lejeune or civilian workers on base, there was no evidence for associations reported between either working or living at Camp Lejeune, or TCE, PCE, benzene, or vinyl chloride exposures at Camp Lejeune, and bladder cancer. Almost all risk estimates were statistically null and close to 1. The few reported statistically significant risk estimates were not reported across other analyses of the Camp Lejeune population. These studies also had several methodological limitations, including a high likelihood of exposure misclassification and a lack of adjustment for smoking in all studies except ATSDR (2018a), and the potential for selection bias in ATSDR (2018a). Collectively, these studies do not provide evidence for an association between working or living at Camp Lejeune, or exposure to TCE, PCE, benzene, or vinyl chloride on base, and bladder cancer.

The majority of the associations between TCE and bladder cancer in epidemiology studies were null and many were based on a small number of cases or were statistically unstable (based on wide CIs). There was no compelling evidence that supports a dose-response relationship, and each study had several methodological limitations that impacted the interpretation of results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). There is no animal evidence indicating TCE can cause bladder cancer, or any proposed MoA with sufficient scientific support. Government and other agencies have either concluded that the scientific evidence is insufficient to make a determination regarding TCE and bladder cancer causation or have not drawn any conclusions. These determinations were based on a limited number of epidemiology studies with inconsistent results, and none of the agencies presented any animal or mechanistic evidence regarding TCE and bladder cancer.

The majority of the associations between PCE and bladder cancer in epidemiology studies were null and many were statistically unstable (based on wide CIs). There was no compelling evidence that supports a dose-response relationship, and each study had several methodological limitations that impacted the interpretation of results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). Animal and MoA evidence does not support causation. In the most recent reviews of the epidemiology evidence, most government and other agencies concluded there is some weak evidence for an association between PCE and bladder cancer, but that evidence is too limited to support causation. None of the agencies presented any animal or mechanistic evidence regarding PCE and bladder cancer.

There is no evidence that benzene causes bladder cancer in animal models, there is no evidence for a plausible MoA, and epidemiology evidence does not support a causal association. Most epidemiology studies reported risk estimates around 1, and statistically significant increased associations were only reported in a few studies with indirect or non-specific exposure measurements. In addition, the epidemiology evidence is based on studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. Government and other agencies have either not reviewed the evidence for benzene and bladder cancer, have not drawn conclusions, or have concluded that there is inadequate or insufficient evidence to evaluate benzene and bladder cancer risk in humans.

Vinyl chloride does not cause bladder cancer in animal models, there is no evidence for a plausible MoA, and epidemiology evidence does not support an association. Most epidemiology studies reported risk estimates that were statistically null and less than 1; statistically significantly increased associations were only reported in a single study that relied on an indirect and non-specific exposure estimate. In addition,

epidemiology evidence is based on studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. No government or international agency reviews of vinyl chloride discussed bladder cancer except for ATSDR (2017a), which concluded there was "below equipoise evidence for [bladder cancer] causation" due to insufficient information.

The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and bladder cancer. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to *trans*-1,2-dichloroethene…were located."

Based on the currently available evidence, I conclude, to a reasonable degree of scientific certainty that TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE in Camp Lejeune drinking water did not cause bladder cancer. I reserve the right to update or amend the opinions contained herein based on new or additional evidence not currently available.

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Attachment A

Literature Search Methods

A.1 Trichloroethylene and Bladder Cancer

A.1.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated trichloroethylene (TCE) and bladder cancer for various purposes (US EPA, 2011, 2020c; ATSDR, 2017a, 2019a; NTP, 2015; IARC, 2014a). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For TCE and bladder cancer, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016 - November 15, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "Trichloroethylene OR Ethinyl Trichloride OR Trichloroethene OR Trilene OR Trielina" to identify any relevant papers published after the last date of my search through the end of 2023.

A.1.2 PubMed Search Terms

A.1.2.1 Epidemiology

(((((("Trichloroethylene"[Mesh] OR trichloroethylene OR TCE[ti]) OR (79-01-06[EC/RN Number]) OR (1,1-Dichloro-2-chloroethylene[tiab] OR 1-Chloro-2,2-dichloroethylene[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR Dow-Tri[tiab] OR Dukeron[tiab] OR (Ethene[tiab] AND trichloro[tiab]) OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab] AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR Fleck-Flip[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR TRIC[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR Tri-Plus[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab]))) AND (("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2])) AND (("Humans"[MeSH] OR human OR humans OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "epidemiology" [Subheading]) NOT (mice OR mouse OR rat OR rats OR rodent)))

A.1.2.2 Animal Carcinogenicity and Mode of Action

(((((("Trichloroethylene"[Mesh] OR trichloroethylene OR TCE[ti]) OR (79-01-06[EC/RN Number]) OR (1,1-Dichloro-2-chloroethylene[tiab] OR 1-Chloro-2,2-dichloroethylene[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR Dow-Tri[tiab] OR Dukeron[tiab] OR (Ethene[tiab] AND trichloro[tiab]) OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab]

AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR Fleck-Flip[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR TRIC[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR Tri-Plus[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab]))) AND ((((toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh])) OR ((mechanistic* OR mechanism* OR "mode of action")))) AND (("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2])))

A.1.3 Scopus Search Terms

A.1.3.1 Epidemiology

(((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce OR tte) OR CASREGNUMBER (79-01-6)) OR TITLE-ABS-KEY ({1,1-Dichloro-2-chloroethylene} OR {1-Chloro-2,2-dichloroethylene} OR anamenth OR benzinol OR blacosolv OR cecolene OR chlorilen OR chlorylea OR circosolv OR crawhaspo OR densinfluat OR {Dow-Tri} OR dukeron OR (ethene AND trichloro) OR {Ethinyl-trichloride} OR (ethylene AND trichloro) OR {Ethylene-trichloride} OR {Fleck-Flip} OR fluate OR lanadin OR lethurin OR narcogen OR narkosoid OR nialk OR petzinol OR triaso OR tric OR trichlorethene OR trichloroethene OR trichloroethylene OR trike OR trilene OR {Tri-Plus} OR vestrol OR vitran OR trichlororan))) AND (TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND (TITLE-ABS-KEY (human OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR {cohort study} OR {case-control} OR {case control} OR {case report} OR {retrospective study} OR {longitudinal study} OR {observational study} OR {cross-sectional study} OR resident*))

A.1.3.2 Animal Carcinogenicity and Mode of Action

(((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce OR tte) OR CASREGNUMBER (79-01-6)) OR TITLE-ABS-KEY ({1,1-Dichloro-2-chloroethylene} OR {1-Chloro-2,2-dichloroethylene} OR anamenth OR benzinol OR blacosolv OR cecolene OR chlorilen OR chlorylea OR circosolv OR crawhaspo OR densinfluat OR {Dow-Tri} OR dukeron OR (ethene AND trichloro) OR {Ethinyl-trichloride} OR (ethylene AND trichloro) OR {Ethylene-trichloride} OR {Fleck-Flip} OR fluate OR lanadin OR lethurin OR narcogen OR narkosoid OR nialk OR petzinol OR triaso OR tric OR trichlorethene OR trichloroethene OR trichloroethylene OR trike OR trilene OR {Tri-Plus} OR vestrol OR vitran OR trichlororan))) AND (TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND (TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*))

A.2 Perchloroethylene and Bladder Cancer

A.2.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated perchloroethylene (PCE) and bladder cancer for various purposes (US EPA, 2012, 2020a; ATSDR, 2017a, 2019b; IARC, 2014b). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For PCE and bladder cancer, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016 - November 17, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "Perchlorethylene OR Tetrachlorethylene OR Tetrachloroethylene OR Perchloroethylene OR Tetrachloroethene" to identify any relevant papers published after the last date of my search through the end of 2023.

A.2.2 PubMed Search Terms

A.2.2.1 Epidemiology

((((("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0])) AND ("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND (("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR group OR epidemiolog* OR occupation* OR worker* OR cohort OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Study"[tiab:~3] OR "Case Control Studies"[tiab:~3] OR "Retrospective Study"[tiab:~2] OR "Retrospective Studies"[tiab:~2] OR "Longitudinal Study"[tiab:~2] OR "Longitudinal Studies"[tiab:~2] OR "Cross-Sectional Study"[tiab:~3] OR "Cross-Sectional Studies"[tiab:~3] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Persons"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh])))

A.2.2.2 Animal Carcinogenicity and Mode of Action

((((("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0])) AND ("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND ((toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh] OR mechanistic* OR mechanism* OR "mode of action")))

A.2.3 Scopus Search Terms

A.2.3.1 Epidemiology

(TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons)) AND (TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer}))

A.2.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons)) AND (TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND ORIG-LOAD-DATE > 20230111 AND NOT TITLE-ABS-KEY (dog)

A.3 Benzene and Bladder Cancer

A.3.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated benzene and bladder cancer for various purposes (US EPA, 2002; ATSDR, 2007a, 2015, 2017a; IARC, 2018). I then conducted literature searches using PubMed and Scopus. For benzene and bladder cancer, the searches identified all epidemiology, animal carcinogenicity, and mode-of-action studies published through November 16, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "benzene OR BTEX" to identify any relevant papers published after the last date of my search through the end of 2023.

A.3.2 PubMed Search Terms

A.3.2.1 Epidemiology

(("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND ((71-43-2[EC/RN Number] OR ("Benzene"[Mesh] OR "benzene"[Title/Abstract])) AND (("Humans"[MeSH] OR human OR humans OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "epidemiology" [Subheading]) NOT (mice OR mouse OR rat OR rats OR rodent)))

A.3.2.2 Animal Carcinogenicity and Mode of Action

(("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND ((71-43-2[EC/RN Number] OR ("Benzene"[Mesh] OR "benzene"[Title/Abstract])) AND ((((toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold Toxicological Concern"[Title/Abstract:~3] OR "Toxicological Concern"[Title/Abstract:~2] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System

Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh])) OR ((mechanistic* OR mechanism* OR "mode of action")))))

A.3.3 Scopus Search Terms

A.3.3.1 Epidemiology

(TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND (KEY (benzene) OR TITLE (benzene) OR CASREGNUMBER (71-43-2)) AND (TITLE-ABS (child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR epidemiolog* OR occupation* OR worker* OR cohort OR {cohort study} OR {case-control} OR {case control} OR {case report} OR {retrospective study} OR {longitudinal study} OR {observational study} OR {cross-sectional study} OR resident*) OR TITLE (human) OR KEY (epidemiology))

A.3.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND (KEY (benzene) OR TITLE (benzene) OR CASREGNUMBER (71-43-2)) AND (TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*))

A.4 Vinyl Chloride and Bladder Cancer

A.4.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated vinyl chloride and bladder cancer for various purposes (US EPA, 2000a,c; ATSDR, 2006, 2016, 2017a; IARC, 2012). I then conducted literature searches using PubMed and Scopus. For vinyl chloride and bladder cancer, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published through November 16, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "vinyl chloride" to identify any relevant papers published after the last date of my search through the end of 2023.

A.4.2 PubMed Search Terms

A.4.2.1 Epidemiology

(("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND ((((("Vinyl Chloride"[Mesh] OR "Vinyl chloride" OR Chloroethene OR chloroethylene OR "1-chloroethylene"[Title/Abstract:~0] OR "ethylene monochloride" OR "monovinyl chloride" OR monochloroethene OR monochloroethylene OR Trovidur OR 75-01-4[EC/RN Number])))) AND (("Humans"[MeSH] OR human OR humans OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "epidemiology" [Subheading]) NOT (mice OR mouse OR rat OR rats OR rodent)))

A.4.2.2 Animal Carcinogenicity and Mode of Action

("Urinary Bladder Neoplasms"[MeSH Terms] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]) AND (("vinyl chloride"[MeSH Terms] OR "vinyl chloride" OR ("chloroethenes" OR "vinyl chloride"[MeSH Terms] OR ("vinyl" AND "chloride") OR "vinyl chloride" OR "chloroethene") OR ("chloroethylenes" OR "vinyl chloride"[MeSH Terms] OR ("vinyl" AND "chloride") OR "vinyl chloride" OR "chloroethylene") OR "1-chloroethylene"[Title/Abstract:~0] OR (("ethylen" OR "ethylene"[Supplementary Concept] OR "ethylene" OR "ethylenes"[MeSH Terms] OR "ethylenes" OR "ethylene s" OR "ethylenic") AND ("monochloride" OR "monochlorides")) OR ("monovinyl" AND ("chlorid" OR "chlorides"[MeSH Terms] OR "chlorides" OR "chloride")) OR "monochloroethene" OR "monochloroethylene" OR "Trovidur" OR "75-01-4"[EC/RN Number]) AND ("toxic" OR "toxical" OR "toxically" OR "toxicant" OR "toxicant s" OR "toxicants" OR "toxicated" OR "toxication" OR "toxicities" OR "toxicity"[MeSH Subheading] OR "toxicity" OR "toxicity s" OR "toxics" OR "toxicolog*" OR ("toxic" OR "toxical" OR "toxically" OR "toxicant" OR "toxicant s" OR "toxicants" OR "toxicated" OR "toxication" OR "toxicities" OR "toxicity"[MeSH Subheading] OR "toxicity" OR "toxicity s" OR "toxics") OR ("toxic" OR "toxical" OR "toxically" OR "toxicant" OR "toxicant s" OR

"toxicants" OR "toxicated" OR "toxication" OR "toxicities" OR "toxicity"[MeSH Subheading] OR "toxicity" OR "toxicity s" OR "toxics") OR "carcinogen*" OR ("carcinogenesis"[MeSH Terms] OR "carcinogenesis" OR "carcinogeneses") OR "cardiotox*" OR ("Pharmacokinetics"[MeSH Terms] OR "Pharmacokinetics" OR "toxicokinetic" OR "Pharmacokinetics"[MeSH Subheading] OR "Toxicokinetics" OR "Toxicokinetics"[MeSH Terms]) OR ("carcinogen s" OR "carcinogenes" OR "carcinogenic" OR "carcinogenically" OR "carcinogenicities" OR "carcinogenicity" OR "carcinogenity" OR "carcinogenous" OR "carcinogens"[Pharmacological Action] OR "carcinogens"[MeSH Terms] OR "carcinogens" OR "carcinogen") OR ("embryolethal" OR "embryolethality") OR "embryotox*" OR ("teratogenesis"[MeSH Terms] OR "teratogenesis" OR "teratogenicity" OR "teratogenic" OR "teratogenically" OR "teratogenity" OR "teratogenous" OR "Teratogens"[Pharmacological Action] OR "Teratogens"[MeSH Terms] OR "Teratogens" OR "teratogen") OR "terato*" OR ("Mutagenesis"[MeSH Terms] OR "Mutagenesis" OR "mutageneses") OR "Gene mutation" OR "Chromosome aberration" OR ("aneuploidy"[MeSH Terms] OR "aneuploidy" OR "aneuploidies") OR ("polyploidy"[MeSH Terms] OR "polyploidy" OR "polyploidies") OR "neurotox*" OR "nephrotox*" OR "immunotox*" OR "hepatotox*" OR "epigenetic*" OR "genotox*" OR "cytotox*" OR "Lethal dose" OR "PBPK" OR ("pharmacokinetic" OR "pharmacokinetical" OR "pharmacokinetically" OR "Pharmacokinetics"[MeSH Subheading] OR "Pharmacokinetics" OR "Pharmacokinetics"[MeSH Terms]) OR "dose response" OR "reference dose" OR "poison*" OR ("poisoned" OR "poisoning"[MeSH Terms] OR "poisoning" OR "poisonings" OR "poisoning"[MeSH Subheading] OR "poisonous" OR "Poisons"[Pharmacological Action] OR "Poisons"[MeSH Terms] OR "Poisons" OR "poison") OR "mutagen*" OR "Lethal Dose 50"[MeSH Terms] OR "Poisons"[MeSH Terms] OR "Pharmacokinetics"[MeSH Terms] OR "Threshold Toxicological Concern"[Title/Abstract:~3] OR "Toxicological Concern"[Title/Abstract:~2] OR "toxicity"[MeSH Subheading] OR "No-Observed-Adverse-Effect Level"[MeSH Terms] OR ("No-Observed-Adverse-Effect Level"[MeSH Terms] OR ("no observed adverse effect" AND "level") OR "No-Observed-Adverse-Effect Level" OR "noael" OR "noaels") OR "Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[MeSH Terms] OR "Maximum Tolerated Dose"[MeSH Terms] OR "Cardiotoxicity"[MeSH Terms] OR "Pharmacokinetics"[MeSH Subheading] OR "Toxicokinetics"[MeSH Terms] OR "Teratogens"[MeSH Terms] OR "Mutagenesis"[MeSH Terms] OR "genes, suppressor"[MeSH Terms] OR "Chromosome Aberrations"[MeSH Terms] OR "birth weight/drug effects"[MeSH Terms] OR "cardiovascular diseases/chemically induced"[MeSH Terms] OR "digestive system diseases/chemically induced"[MeSH Terms] OR "endocrine system diseases/chemically induced"[MeSH Terms] OR "pregnancy complications/chemically induced"[MeSH Terms] OR "eye diseases/chemically induced"[MeSH Terms] OR "hemic and lymphatic diseases/chemically induced"[MeSH Terms] OR "immune system diseases/chemically induced"[MeSH Terms] OR "LC50"[Title/Abstract] OR "neoplasms/chemically induced"[MeSH Terms] OR "nervous system diseases/chemically induced"[MeSH Terms] OR "nervous system diseases/chemically induced"[MeSH Terms] OR "skin and connective tissue diseases/chemically induced"[MeSH Terms] OR "terata*" OR ("teratogenesis"[MeSH Terms] OR "teratogenesis") OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "toxicol*"[Journal] OR "reproductive and urinary physiological phenomena/drug effects"[MeSH Terms] OR ("mechanistic*" OR "mechanism*" OR "mode of action"))) AND 2016/01/01:3000/12/31[Date - Publication]

A.4.3 Scopus Search Terms

A.4.3.1 Epidemiology

(TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND ((TITLE-ABS-KEY ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR monochloroethylene OR trovidur) OR CASREGNUMBER (75-01-4))) AND

(TITLE-ABS (child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR epidemiolog* OR occupation* OR worker* OR cohort OR {cohort study} OR {case-control} OR {case control} OR {case report} OR {retrospective study} OR {longitudinal study} OR {observational study} OR {cross-sectional study} OR resident*) OR TITLE (human) OR KEY (epidemiology))

A.4.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})) AND ((TITLE-ABS-KEY ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR monochloroethylene OR trovidur) OR CASREGNUMBER (75-01-4))) AND (TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*))

A.5 Trans-1,2-Dichloroethylene and Bladder Cancer

A.5.1 Publication Date Range

I conducted literature searches using PubMed and Scopus for epidemiology, animal carcinogenicity, and mode-of-action studies published through May 06, 2024.

A.5.2 PubMed Search Terms

A.5.2.1 Epidemiology

("trans-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethylene"[tiab:~0] OR "trans-Acetylene dichloride"[tiab:~0] OR "trans-1,2-Dichloroethylene"[tiab:~0] OR "trans-Dichloroethylene"[tiab:~0] OR 156-60-5[EC/RN Number])

("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Study"[tiab:~2] OR "Case Control Studies"[tiab:~2] OR "Retrospective Study"[tiab:~2] OR "Retrospective Studies"[tiab:~2] OR "Longitudinal Study"[tiab:~2] OR "Longitudinal Studies"[tiab:~2] OR "Cross-Sectional Study"[tiab:~3] OR "Cross-Sectional Studies"[tiab:~3] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh])

"Kidney Neoplasms"[Mesh] OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Carcinoma, Renal Cell"[Mesh] OR "Renal Cell Carcinoma"[tiab:~3] OR "Nephroma, Mesoblastic"[Mesh] OR "Wilms Tumor"[Mesh]

"Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]

("Leukemia"[Mesh] OR leukemia[Title/Abstract])

"Lymphoma, Non-Hodgkin"[Mesh] OR "Non-Hodgkin's Lymphoma"[tiab:~0] OR "Non-Hodgkin Lymphoma"[tiab:~0]

A.1.2.2 Animal Carcinogenicity and Mode of Action

("trans-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethylene"[tiab:~0] OR "trans-Acetylene dichloride"[tiab:~0] OR "trans-1,2-Dichloroethylene"[tiab:~0] OR "trans-Dichloroethylene"[tiab:~0] OR 156-60-5[EC/RN Number])

(toxicity OR toxicolog* OR toxicology OR toxic* OR "Toxicology"[Mesh] OR carcinogen* OR Carcinogenesis OR "Carcinogenesis"[Mesh] OR cancer*[Title/Abstract] OR "Neoplasms"[Mesh] OR neoplasm* OR tumor* OR cardiotox* OR "Cardiotoxins"[Mesh] OR Cardiotoxicity OR "Cardiotoxicity"[Mesh] OR Toxicokinetics OR "Pharmacokinetics"[Mesh] OR carcinogenicity OR embryolethality OR embryotoxicity OR Teratogenicity OR "Teratogenesis"[Mesh] OR Terato* OR mutagenesis OR "Mutagenesis"[Mesh] OR "Gene mutation" OR "Chromosome aberration" OR "Chromosome Aberrations"[Mesh] OR Aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Reproductive Health"[Mesh] OR DNA OR mutagen* OR mechanistic* OR mechanism* OR "mode of action" OR "oxidative stress" OR inflammat*)

"Kidney Neoplasms"[Mesh] OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Carcinoma, Renal Cell"[Mesh] OR "Renal Cell Carcinoma"[tiab:~3] OR "Nephroma, Mesoblastic"[Mesh] OR "Wilms Tumor"[Mesh]

"Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]

("Leukemia"[Mesh] OR leukemia[Title/Abstract])

"Lymphoma, Non-Hodgkin"[Mesh] OR "Non-Hodgkin's Lymphoma"[tiab:~0] OR "Non-Hodgkin Lymphoma"[tiab:~0]

A.1.3 Scopus Search Terms

A.1.3.1 Epidemiology

TITLE-ABS-KEY ({trans-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethylene} OR {trans-Acetylene dichloride} OR {trans-1,2-Dichloroethylene} OR {trans-Dichloroethylene}) OR CASREGNUMBER (156-60-5)

TITLE-ABS-KEY (human OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "cohort stud*" OR "case-control stud*" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR resident*)

TITLE-ABS-KEY ("Kidney Neoplasms" OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Renal Cell Carcinoma" OR "Nephroma, Mesoblastic" OR "Wilms Tumor")

TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})

TITLE-ABS-KEY (Leukemia)

TITLE-ABS-KEY ("Non-Hodgkin's Lymphoma*" OR "Non-Hodgkin Lymphoma*" OR "Lymphoma, Non-Hodgkin" OR "Lymphoma, Non-Hodgkin's" OR {Non-Hodgkin's} OR {Non Hodgkin's} OR {Non-Hodgkin} OR {Non Hodgkin})

A.1.3.2 Animal Carcinogenicity and Mode of Action Search Terms

TITLE-ABS-KEY ({trans-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethylene} OR {trans-Acetylene dichloride} OR {trans-1,2-Dichloroethylene} OR {trans-Dichloroethylene}) OR CASREGNUMBER (156-60-5)

(TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action" OR "oxidative stress" OR inflammat*) OR SRCTITLE (toxciol*)

TITLE-ABS-KEY ("Kidney Neoplasms" OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Renal Cell Carcinoma" OR "Nephroma, Mesoblastic" OR "Wilms Tumor")

TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})

TITLE-ABS-KEY (Leukemia)

TITLE-ABS-KEY ("Non-Hodgkin's Lymphoma*" OR "Non-Hodgkin Lymphoma*" OR "Lymphoma, Non-Hodgkin" OR "Lymphoma, Non-Hodgkin's" OR {Non-Hodgkin's} OR {Non Hodgkin's} OR {Non-Hodgkin} OR {Non Hodgkin})

Attachment B

Camp Lejeune Epidemiology Studies

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Table B.1 Camp Lejeune Cohort Study Characteristics

Study	Study Population				Exposure Characterization		Cancer Outcome			
	Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Bove *et al.* (2014b)	Marines & Navy personnel	B	CL & CP: 20-49[a]	CL: 154,932, CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Bladder	SSA and NDI	1979-2008
Bove *et al.* (2014a)	Civilian employees	B	CL: 31-58[a] CP: 34-60[a]	CL: 4,647, CP: 4,690	1973-1985	Employment at base	Mort	Bladder	SSA and NDI	1979-2008
ATSDR (2018)[b]	Marines & Navy personnel and civilian employees	B	Marines & Navy Personnel CL and CP: 50-54[c] Civilian Employees CL: 60-64[c], CP: ≥65[c]	Marines & Navy Personnel CL: 50,684, CP: 8,615 Civilian Employees CL: 2,168, CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines & Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Bladder	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Study	Study Population				Exposure Characterization		Cancer Outcome			
	Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Bove *et al.* (2024b)	Marines & Navy personnel and civilian employees	B	Marines & Navy Personnel All 1975-1985 CL: $\bar{x}$ = 37.3 CP: $\bar{x}$ = 37.8 Began Active Duty 1975-1985 CL: $\bar{x}$ = 35.0 CP: $\bar{x}$ = 35.2 Civilian Employees CL: $\bar{x}$ = 52.9 CP: $\bar{x}$ = 55.1	Marines & Navy Personnel All 1975-1985 CL: 208,063 CP: 225,999 Began Active Duty 1975-1985 CL: 154,821 CP: 163,484 Civilian Employees CL: 6,494 CP: 5,797	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Assignment/ employment at base	Inc	Urinary bladder - Malignant & *In situ*; PTCC; NPTCC; Urothelial	SSA Data for Epidemiological Researchers, NDI, and cancer registries (state, territory, DOD, and VA)	1996-2017

Study	Study Population				Exposure Characterization		Cancer Outcome			
	Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Bove *et al.* (2024a)	Marines & Navy personnel and civilian employees	B	Marines & Navy Personnel All 1975-1985 CL: $\bar{x}$ = 22.1 CP: $\bar{x}$ = 22.4 Began Active Duty 1975-1985 CL: $\bar{x}$ = 20.2 CP: $\bar{x}$ = 20.5 Civilian Employees CL: $\bar{x}$ = 39.1 CP: $\bar{x}$ = 41.2	Marines & Navy Personnel All 1975-1985 CL: 219,988 CP: 232,0126 Began Active Duty 1975-1985[d] CL: 159,128 CP: 168,406 Civilian Employees CL: 7,332 CP: 6,677	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Assignment/ employment at base	Mort	Urinary bladder	SSA Data for Epidemiological Researchers and NDI	1979-2018

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; DoD = Department of Defense; Inc = Incidence; Mort = Mortality; NDI = National Death Index; NPTCC = Non-PTCC Transitional Cell Carcinoma; PTCC = Papillary Transitional Cell Carcinoma; SSA = Social Security Administration; US = United States; VA = Veterans Affairs; $\bar{x}$ = Mean; Yrs = Years.
(a) Median age from start to end of follow-up (Bove *et al.*, 2014a,b).
(b) Ages and population sizes are reflective of Marines, Navy, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018a).
(c) Median age at survey or death (ATSDR, 2018a).
(d) Bove *et al.* (2024b) reported that this subgroup consisted of 154,821 Camp Lejeune and 163,484 Camp Pendleton Marines and Navy personnel in the methods section. However, the abstract and tables report 159,128 Camp Lejeune and 168,406 Camp Pendleton Marines and Navy personnel.

Table B.2 Employment/Assignment at Camp Lejeune and Bladder Cancer Camp Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-Cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	US general population	Mort	SMR	**Marines & Navy Personnel**					Age, sex, race, and calendar period
				All	11	13.04	0.84 (0.42-1.51)	–	
	CP Marines & Navy personnel		HR	All (10-yr lag)	11	–	0.76 (0.34-1.71)		Age, sex, race, rank, and education
Bove *et al.* (2014a)	US general population	Mort	SMR	**Civilian Employees**					Age, sex, race, and calendar period
				All	2	3.76	0.53 (0.06, 1.92)	–	
	CP civilian employees		HR	All (10-yr lag)	2	–	0.65 (0.12-3.65)		Age, sex, race, blue- or white-collar occupation, and education
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**Marines & Navy Personnel**					Age
				All	182	–	**1.64 (1.02-2.64)**	–	
	CP civilian employees			**Civilian Employees**					
				All	13	–	0.82 (0.37-1.84)	–	
Bove *et al.* (2024b)	CP Marines & Navy personnel	Inc	HR	**Marines & Navy Personnel**					Age, sex, race, rank, and education level
				Urinary bladder					
				Began active duty between 1975-1985	444	–	1.09 (0.95-1.24)	–	
				All	1,001		1.05 (0.96-1.14)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	238	–	1.02 (0.87-1.20)	–	
				Medium (7-10)	109		1.18 (0.95-1.46)		
				High (>10)	97		1.20 (0.94-1.52)		
				PTCC					
				Began active duty between 1975-1985	320	–	1.08 (0.93-1.26)	–	
				All	712		1.09 (0.98-1.21)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	168	–	0.99 (0.82-1.19)	–	
				Medium (7-10)	83		1.25 (0.98-1.59		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-Cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				High (>10)	69		1.19 (0.89-1.58)		
				NPTCC					
				Began active duty between 1975-1985	109	–	1.11 (0.85-1.46)	–	
				All	257		0.99 (0.83-1.17)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	62	–	1.13 (0.82-1.56)	–	
				Medium (7-10)	24		1.05 (0.67-1.65)		
				High (>10)	23		1.11 (0.67-1.82)		
				Urothelial					
				Began active duty between 1975-1985	429	–	1.09 (0.95-1.25)	–	
				All	969		1.06 (0.97-1.16)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	230	–	1.02 (0.87-1.20)	–	
				Medium (7-10)	107		1.20 (0.97-1.48)		
				High (>10)	92		1.17 (0.91-1.50)		
				Bladder – malignant					
				All	497	–	0.99 (0.87-1.11)	–	
				Bladder – in-situ					
				All	524	–	1.11 (0.98-1.25)	–	
	CP civilian workers			**Civilian Employees**					Age, sex, race, blue collar work, and education level
				Type of bladder cancer					
				Urinary Bladder	87	–	1.10 (0.81-1.50)	–	
				PTCC	60		1.07 (0.74-1.56)		
				NPTCC	24		1.30 (0.70-2.40)		
				Urothelial	84		1.13 (0.82-1.55)		
				Bladder – malignant	49		1.14 (0.76-1.73)		
				Bladder-in-situ	40		1.09 (0.69-1.73)		
				Type of bladder cancer and duration of employment (quarter yrs)					
				Urinary bladder					

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-Cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				Low/medium (1-21)	46	–	1.18 (0.80-1.75)	–	
				High (>21)	41		1.09 (0.69-1.71)		
				PTCC					
				Low/medium (1-21)	33	–	1.16 (0.73-1.84)	–	
				High (>21)	27		1.06 (0.61-1.83)		
				NPTCC					
				Low/medium (1-21)	12	–	1.51 (0.68-3.37)	–	
				High (>21)	12		1.28 (0.55-2.96)		
				Urothelial					
				Low/medium (1-21)	45	–	1.23 (0.83-1.84)	–	
				High (>21)	39		1.09 (0.69-1.73)		
Bove *et al.* (2024a)[b]	US general population	Mort	SMR	**Marines & Navy Personnel**					Age, sex, race, and calendar period
				Began active duty between 1975-1985	61	–	0.97 (0.74-1.24)	–	
				All	137		0.90 (0.76-1.07)		
	CP Marines & Navy personnel		RR	Began active duty between 1975-1985	61		1.02 (0.71-1.45)		Age, sex, and race
				All	137		0.90 (0.72-1.13)		
			HR	Began active duty between 1975-1985	61		1.02 (0.72-1.45)		Age, sex, race, rank, and education level
				All	137		0.89 (0.71-1.11)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	1.02 (0.61-1.73)	–	
				Medium (>2-7)			0.80 (0.46-1.38)		
				High (>7)			1.24 (0.78-1.96)		
	US general population		SMR	**Civilian Employees**					Age, sex, race, and calendar period
	CP civilian workers			All	18	–	0.85 (0.50-1.34)	–	
			RR		18		0.65 (0.34-1.24)		Age, sex, and race
			HR		18		0.65 (0.34-1.26)		Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low (1-5)	–	–	1.76 (0.70-4.40)	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-Cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				Medium (6-22)			0.47 (0.16-1.37)		
				High (23-53)			0.45 (0.19-1.06)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; NPTCC = Non-Papillary Transitional Cell Carcinoma; OR = Odds Ratio; PTCC = Papillary Transitional Cell Carcinoma; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; US = United States; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al.* (2024a) also ran analyses based on contributing causes, which I do not report here.

Table B.3 TCE Exposure at Camp Lejeune and Bladder Cancer Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-3,100)[a]	4	–	0.81 (0.26-2.50)	–	
				Medium/high (>3,100-8,585)[a]	7		0.84 (0.34-2.10)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-3,100)	0		0.00		
				Medium (>3,100-7,700)	5		2.69 (0.63-11.46)		
				High (>7,700-39,745)	2		0.92 (0.15-5.55)		
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**Marines & Navy personnel[c]**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low (<110)	88	–	1.28 (0.76-2.15)	–	
				Medium (110-<11,030)	83		1.68 (1.00-2.82)		
				High (≥11,030)	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)			Medium (110-<11,030)	83		1.34 (0.98-1.85)		
				High (≥11,030)	11		0.74 (0.39-1.43)		
	CP civilian employees			**Civilian Employees[e]**					None
				Cumulative exposure level (µg/L-mos)[d]					
				Low (<10,868)	8	–	1.02 (0.41-2.54)	–	
				Medium (10,868-<50,563)	2		0.32 (0.07-1.45)		
				High (≥50,563)	3		1.81 (0.50-6.53)		
	CL civilian employees with low exposure (<10,868 µg/L-mos)			Medium (10,868-<50,563)	2		0.32 (0.07-1.50)		
				High (≥50,563)	3		1.78 (0.47-6.77)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; OR = Odds Ratio; PCE = Tetrachloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yrs = Years.

– = Not Reported.

(a) Exposure groups are unclear in Bove *et al*. (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.

(b) To evaluate exposure-response relationships, Bove *et al*. (2014b) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.

(c) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018a).

(d) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (3,948 µg/L-mos) and 90th (7,863 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018a).

(e) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018a).

Table B.4 PCE Exposure at Camp Lejeune and Bladder Cancer Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-155)[a]	4	–	0.75 (0.24-2.33)	–	
				Medium/high (>155-8,585)[a]	7		0.89 (0.35-2.22)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-155)	1		0.55 (0.06-5.35)		
				Medium (>155-380)	3		1.62 (0.32-8.10)		
				High (>380-8,585)	3		1.24 (0.25-6.21)		
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[c]					
				Low (0-<36)	93	–	1.33 (0.80-2.24)	–	
				Medium (36-<711)	59		1.30 (0.76-2.23)		
				High (≥711)	30		**2.07 (1.12-3.82)**		
	CL Marines & Navy personnel with low exposure (>0-<36 µg/L-mos)			Medium (36-<711)	59		0.99 (0.69-1.40)		
				High (≥711)	30		1.54 (0.99-2.41)		
	CP civilian employees			**Civilian Employees[d]**					None
				Low (<457)	8	–	1.02 (0.41-2.54)	–	
				Medium (457-<2,118)	2		0.32 (0.07-1.45)		
				High (≥2,118)	3		1.81 (0.50-6.53)		
	CL civilian employees with low exposure (<457 µg/L-mos)			Medium (457-<2,118)	2		0.32 (0.07-1.50)		
				High (≥2,118)	3		1.78 (0.47-6.77)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; OR = Odds Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.

(a) Exposure groups are unclear in Bove *et al*. (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, Bove *et al*. (2014b) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(c) ATSDR (2018a) categorized as low exposure (< 50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile) ; for female Marines and Navy personnel, cut points were based on the 75th (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos.
(d) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018a).

Table B.5 Benzene Exposure at Camp Lejeune and Bladder Cancer Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-45)[a]	3	–	0.52 (0.15-1.85)	–	
				Medium/high (>45-601)[a]	8		1.07 (0.44-2.60)		
	CL Marines & Navy personnel with exposure <2 µg/L-mos[b]			Low (2-45)	0		0.00		
				Medium (>45-110)	5		4.04 (0.77-21.18)		
				High (>110-601)	3		2.26 (0.37-13.78)		
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**Marines & Navy Personnel[c]**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low	88	–	1.28 (0.76-2.15)	–	
				Medium	83		1.68 (1.00-2.82)		
				High	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure[d]			Medium	83		1.34 (0.98-1.85)		
				High	11		0.74 (0.39-1.43)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; OR = Odds Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yrs = Years.
– = Not Reported.
(a) Exposure groups are unclear in Bove *et al.* (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, Bove *et al.* (2014b) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(c) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018a).
(d) ATSDR (2018a) categorized as low exposure (<50th percentile), medium exposure (≥5^{0th} percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018a).

Table B.6 Vinyl Chloride Exposure at Camp Lejeune and Bladder Cancer Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-205)[a]	4	–	0.75 (0.24-2.34)	–	
				Medium/high (>205-2,800)[a]	7		0.88 (0.35-2.22)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-205)	0		0.00		
				Medium (>205-500)	5		2.59 (0.61-10.98)		
				High (>500-2,800)	2		0.91 (0.15-5.52)		
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**Marines & Navy Personnel[c]**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low	88	–	1.28 (0.76-2.15)	–	
				Medium	83		1.68 (1.00-2.82)		
				High	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure[d]			Medium	83		1.34 (0.98-1.85)		
				High	11		0.74 (0.39-1.43)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; OR = Odds Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yrs = Years.
– = Not Reported.
(a) Exposure groups are unclear in Bove *et al.* (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text says, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, Bove *et al.* (2014b) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(c) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018a).
(d) ATSDR (2018a) categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018a).

Attachment C

Epidemiology Study Quality Assessment

List of Tables

Table C.1 Bladder Cancer Epidemiology Study Quality Assessment

Table C.1 Bladder Cancer Epidemiology Study Quality Assessment

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Cohort Studies										
Wong (1987a,b)	Male chemical workers			B		<u>Strengths</u> ▪ Appropriate study and comparison groups ▪ 2.3% loss to follow-up <u>Weaknesses</u> ▪ Unknown number of exclusions	<u>Strengths</u> ▪ Semiquantitative exposure estimate (*i.e.*, considered frequency, duration, and intensity) ▪ No missing data ▪ Assessed time-varying nature of exposure <u>Weaknesses</u> ▪ Indirect chemical exposure measurement (*i.e.*, work location/type of work, and uniform task approach)	<u>Strengths</u> ▪ Deaths identified using reliable sources (company records, SSA, DMV, death certificates) ▪ 32 yrs of follow-up <u>Weaknesses</u> ▪ Assessed mortality only ▪ 2.2% of all deaths without death certificate (1.1% in continuously exposed group, 1.3% in intermittently exposed group, 4.3% in unexposed group)	<u>Strengths</u> ▪ Controlled for: age, sex, and race <u>Weaknesses</u> ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ About 8% missing race (assumed white)	<u>Strengths</u> ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, 10, 10-19 and 20 years) <u>Weaknesses</u> ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Garabrant *et al.* (1988)	Aircraft manufacturing workers	T				Strengths ▪ Appropriate study and comparison groups ▪ No exclusions for missing data Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.* factory personnel records) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, California DMV, credit records, death certificates, California Death Tapes) ▪ 25 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for age, sex, and race Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Race was missing for unspecified number of subjects; assumed to be white	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, ≥ 4-years employment in duration analysis) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Shannon *et al.*, (1988)	Lamp manufacturing workers	T				Strengths ▪ Appropriate study and comparison groups ▪ About 16.5% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work location in plant) ▪ Qualitative exposure estimate (*i.e.*, ever/never) ▪ Amount of missing data unknown ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases were identified using a reliable source (*i.e.*, provincial cancer registry) ▪ Assessed disease incidence ▪ 19 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Blair *et al.* (1989)	Coast Guard officers and personnel	T	P	B		Strengths ▪ Appropriate study and comparison groups ▪ <5% loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job title) ▪ Qualitative exposure estimate (*i.e.*, by job title) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, Coast Guard, VA, SSA, credit, and DMV records, and death certificates) ▪ 39 yrs of follow-up Weaknesses ▪ Assessed disease mortality only ▪ ≈2% of deaths had no death certificate; unclear how this was addressed	Strengths ▪ Controlled for: age, sex, and race Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or occupational history ▪ 8% missing race data (assumed white)	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Costa *et al.* (1989)	Aircraft manufacturing workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <2% loss to follow-up; no exclusions Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, occupational history at factory) ▪ Did not account for time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, local registries and death certificates) ▪ 28 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (5- and 15-yr lags) Weaknesses ▪ No major weaknesses
Teta *et al.* (1990)	Hourly male employees of the Union Carbide Corporation's Chemicals and Plastics business group				V	Strengths ▪ Appropriate study group ▪ <1.1% of entire cohort lost to follow-up Weaknesses ▪ Inappropriate comparison group (*i.e.*, white and non-white employee mortality compared to white-only population) ▪ Unknown number of exclusions	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurements (*i.e.*, business group) ▪ Qualitative exposure estimate (*i.e.*, employment in group) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, NDI, company mortality register, benefit records, and death certificates) ▪ 10 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Dagg *et al.* (1992)	Employees at oil refineries, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 4.8% loss to follow-up; <1% excluded from individual refinery analyses (*i.e.*, worked at both refineries under study) Weaknesses ▪ All women excluded (4.8% of total) due too few cases	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, based on work history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, California death index, Equifax, and death certificates) ▪ 37 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*e.g.*, analyses based on 10-19, 20-29, and ≥30 yrs since hire Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sinks *et al.* (1992)	Paperboard printing plant workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <2% excluded in SMR analyses and <16% excluded in SIR analyses Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment at facility) ▪ Qualitative exposure estimate (*i.e.*, ever/never) ▪ Did not assess time-varying nature of exposure	Strengths ▪ All deaths and most incident cases identified and validated using reliable sources (*i.e.*, SSA, mailing address with USPS, death certificates, and local cancer registries) ▪ Assessed disease incidence ▪ 32 yrs of follow-up Weaknesses ▪ Some cases self-reported and not all validated	Strengths ▪ Controlled for: age, sex, and race (SIR analysis) Weaknesses ▪ Did not control for or consider: race/ethnicity (SMR analysis), smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ 15% missing race data; assumed white	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Tsai *et al.* (1993)	Male refinery/ petrochemical workers, US			B		Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect benzene exposure measurement (*i.e.*, job history) ▪ Qualitative exposure estimate (*i.e.*, ever/never employment) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, NDI, and SSA ▪ 17 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Axelson *et al.* (1994)	TCE-exposed workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <4% excluded Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ Direct chemical exposure measurement (*i.e.*, U-TCA) ▪ No missing data Weaknesses ▪ Qualitative exposure estimate (*i.e.*, ever exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using reliable sources (*i.e.*, Swedish cause-of-death and cancer registries) ▪ Assessed disease incidence ▪ 30 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Anttila *et al.* (1995)	FIOH workers	T				Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up; 7% excluded Weaknesses ▪ No major weaknesses	Strengths ▪ Direct chemical exposure measurement (U-TCA) ▪ No missing data Weaknesses ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using reliable sources (*i.e.*, Population Register Center, Finnish Cancer Registry, and Central Statistical Office of Finland) ▪ Assessed disease incidence ▪ 26 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex) ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (10 and 20-yr lags) Weaknesses ▪ No major weaknesses
Honda *et al.* (1995)	Employees of a petroleum manufacturing plant, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 3% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history at plant) ▪ Qualitative exposure estimate (*i.e.*, ever employment at plant) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, SSA Death Master File, NDI, state DMV records, and death certificates) ▪ 50 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ No missing data Weaknesses ▪ Did not consider or control for: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Collingwood *et al.* (1996)	Workers at an oil refinery, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 2% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company's personnel database, PBI, NDI, SSA, and death certificates) ▪ 41 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity ▪ About 3.5% missing race data; classified as White Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (analyses of 20-29 and 30+ yrs since first employment) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Satin *et al.* (1996)	Workers at an oil refinery, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 5.1% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, personnel annuitant record systems, DMV, SSA, and NDI) ▪ 51 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, analyses of 10-19, 20-29, 30-39 and 40+ yrs since first hired) Weaknesses ▪ No major weaknesses
Lynge *et al.* (1997)	Service station workers in Denmark, Finland, Norway, and Sweden			B		Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job at time of census) ▪ Qualitative exposure estimate (*i.e.*, employment at service station) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, national cancer registries) ▪ Assessed disease incidence ▪ ≥5 yrs follow-up (Denmark: 18 yrs; Finland: 15 yrs; Norway: 21 yrs; Sweden: 20 yrs) Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Morgan *et al.* (1998)	Aircraft manufacturing workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <0.01% excluded Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job classification and JEM) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, NDI, and death certificates) ▪ 44 yrs of follow-up Weaknesses ▪ Assessed mortality only ▪ About 3% of deaths missing death certificates; unclear how this was handled in analysis	Strengths ▪ Controlled for or considered: age and sex (RR analyses) Weaknesses ▪ Did not control for or consider: sex (SMR analyses), smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Considered race but data was "sparse" and was ultimately not used	Strengths ▪ Exposure documented before outcome Weaknesses ▪ Did not consider appropriate latency (6-month lag)

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Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Pukkala (1998)	Employees of a Finnish oil and chemical enterprise			B		Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up/exclusions Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment with enterprise) ▪ Qualitative exposure estimate (*i.e.*, job type) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Finish Cancer Registry) ▪ Assessed disease incidence ▪ 24 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age ▪ No missing data Weaknesses ▪ Did not consider or control for: sex, race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or occupational history ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Bulbulyan *et al.* (1999)	Female Russian printing plant employees			B		Strengths ▪ <20% loss to follow-up (1.5%) and no exclusions Weaknesses ▪ Benzene use in bookbinding was discontinued in 1958, but results stratified by year of first employment are not provided ▪ Comparison rates based only on 1992, not the entire follow-up period	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, personnel records and job type) ▪ Qualitative exposure estimate (*i.e.*, job type) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using a reliable source (*i.e.*, Moscow Vital Statistics Department) ▪ 15 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics or occupation history ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (benzene use discontinued 20 yrs prior) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Consonni *et al.* (1999)	Italian oil refinery workers			B		Strengths ▪ Appropriate study and comparison groups ▪ ≈ 4.3% lost to follow-up and <1% excluded Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect exposure measurement (*i.e.*, based on job histories) ▪ Qualitative exposure estimate (*i.e.*, job history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, population statistics offices and death certificates) ▪ 43 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or occupational history	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Divine *et al.* (1999)	Employees at refineries, petrochemical facilities and research laboratories, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 2.5% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history and job title) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, HCFA, and death certificates) ▪ 47 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity ▪ 1% missing data on sex or race, assumed to be male and/or White Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (had to be employed ≥5 yrs) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Ritz (1999)	Uranium-processing workers	T				Strengths ▪ Appropriate study and comparison groups ▪ 8% excluded Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history and JEM) ▪ Qualitative exposure estimate (*i.e.*, employment at facility) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, NDI, and death certificates) ▪ 39 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Lewis *et al.* (2000a)	Active and terminated workers at three oil refineries and petrochemical facilities			B		Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Unknown loss to follow-up ▪ Unknown number of exclusions	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, company records and work histories) ▪ Qualitative exposure estimate (*i.e.*, employment at plant) ▪ Amount of missing data unknown ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, benefit records, NDI, SSA, and death certificates) ▪ 23 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Hansen *et al.* (2001)	TCE exposed workers	T				Strengths ▪ Appropriate sample and comparison groups Weaknesses ▪ Loss to follow-up unknown; unable to identify individuals for 36% and 48% of urine and air samples, respectively	Strengths ▪ Direct chemical exposure measurement (*i.e.*, U-TCA and occupational air measurements) ▪ No missing data Weaknesses ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Danish Cancer Registry) ▪ Assessed disease incidence ▪ 29 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Appropriate consideration of latency (10- and 20-yr lags) Weaknesses ▪ Exposure not necessarily measured before outcome (exposure period overlaps follow-up period)

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Wong *et al.* (2001a)	Employees at oil refinery, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 1.1% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history from personnel records and payroll files) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA and NDI) ▪ 39 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Hispanics and unknown race were considered white ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, analyses based on 20-39 and 40+ yrs since first exposure; 10-29 and 30+ yrs of employment) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Wong *et al.* (2001b)	Employees at oil refinery, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 1.7% loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history from personnel records and payroll files) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources *(i.e.*, SSA and NDI) ▪ 51 yrs of follow-up Weaknesses Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, analyses based on 20-39 and 40+ yrs since first exposure; 10-29 and 30+ yrs of employment) ▪ Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sorahan *et al.* (2002)	Refinery and petroleum distribution workers, UK			B		Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Unknown loss to follow-up and number of exclusions	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history) ▪ Qualitative exposure estimate (*i.e.*, employment as refinery or distribution worker) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, national registers and death certificates) ▪ 48 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Travier *et al.* (2002)	Dry-cleaning workers	T	P			Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Loss to follow-up and number of exclusions unknown	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported employment and industrial codes from two decennial censuses) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Amount of missing employment data unknown ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases and deaths identified using a reliable source (*i.e.*, CERIII) ▪ Assessed disease incidence ▪ 19 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Chang *et al.* (2003)	Electronics factory workers	T	P			Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-ups or exclusions Weaknesses ▪ Relatively young subjects (mean age 39 yrs at end of follow-up)	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment status at factory) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified and validated using a reliable source (*i.e.*, National Mortality Database) ▪ 13 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Lewis *et al.* (2003)	Canadian refinery/ petrochemical workers			B		Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up Weaknesses ▪ Young study population at cohort inception (M $\bar{x}$= 29.1 M; F $\bar{x}$= 27.5)	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect benzene exposure measurement (*i.e.*, location, department, function, date, and expert review ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Canadian Cancer Data Base) ▪ Deaths identified using a reliable source (*i.e.*, Canadian Mortality Data Base) ▪ Assessed disease incidence ▪ 31 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled: age, sex, smoking Weaknesses ▪ Did not control for: race/ethnicity, prior cancer treatment, chronic bladder inflammation, family history of bladder cancer, genetics, or other potential occupational exposures ▪ >5% missing data	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, analyses by 10+ year exposure duration) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Raaschou-Nielsen *et al.* (2003)	Blue-collar workers at TCE using companies	T				Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ >75% excluded (including an unspecified number of large companies [200+ employees; 24% of companies]; loss to follow-up unknown	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, blue-collar employment) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ 37% of workers with unknown blue- status (only included in sensitivity analyses) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Danish Cancer Registry) ▪ Assessed disease incidence ▪ 30 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ No major strengths Weaknesses ▪ No consideration of latency ▪ Exposure not necessarily documented before outcome (exposure period overlaps follow-up period)
Tsai *et al.* (2003)	Male chemical/ refinery workers US			B		Strengths ▪ Appropriate study and comparison groups ▪ No loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA) ▪ 27 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.* include analyses of employees with ≥ 10 yrs of employment) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Huebner *et al.* (2004)	Employees at two oil refineries and petrochemical facilities, US			B		Strengths ▪ Appropriate study and comparison groups ▪ ≤2% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ ≤1% missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, company records and work histories) ▪ Qualitative exposure estimate (*i.e.*, employment at plant) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, benefits records, NDI, and SSA) ▪ 28 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, and race/ethnicity ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sorahan *et al.* (2005)	Benzene exposed workers			B		Strengths ▪ Appropriate study and comparison group ▪ 5.7% loss to follow-up Weaknesses ▪ Unknown number of exclusions ▪ Follow-up did not end with first cancer incidence	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, personnel officer reports at firms or plants) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases and deaths identified using reliable sources (*i.e.*, ONS and DHSS) ▪ Assessed disease incidence ▪ 31 and 35 yrs of follow-up for incidence and mortality, respectively Weaknesses ▪ Unconfirmed diagnoses for 22 cases	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Zhao *et al.* (2005)	Aerospace workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <1% excluded Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history and JEM) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases and deaths identified using reliable sources (*i.e.*, state cancer registries, company records, SSA, CA vital statistics, NDI records, death certificates) ▪ Assessed disease incidence ▪ 52 and 13 yrs of follow-up for mortality and incidence, respectively Weaknesses ▪ 11% of cancer cases not captured (*i.e.*, occurred outside of state registries covered in this study)	Strengths ▪ Controlled for: age, sex, and all other chemical exposures (*i.e.*, PAHs, benzene, mineral oils, and hydrazine) ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Did not include relevant covariates in a time-varying manner (*i.e.*, other chemical exposures)	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (20-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Boice *et al.* (2006)	Aerospace workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <1% loss to follow-up; ~12% excluded Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job title, personnel listings, and expert opinion) ▪ Qualitative exposure estimate (*i.e.*, every exposed) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, CA death tapes and index, NDI, PBI, SSA, and HCFA files, employment work history cards, pension records, retirement records, and death certificates) ▪ 52 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, race, and co-exposure to hydrazine ▪ 16% missing race data; used weighted approximation based on known racial proportions Weaknesses ▪ Did not consider or control for: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Did not include relevant covariates in a time-varying manner (*i.e.*, hydrazine exposure)	Strengths ▪ Exposure documented before outcome Weaknesses ▪ Did not consider appropriate latency (6-month lag)

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Gun *et al.* (2006)	Employees of the Australian Institute of Petroleum member companies			B		Strengths ▪ Appropriate study and comparison groups ▪ <20% loss to follow-up (1.3% of males and 4.9% of females) Weaknesses ▪ Participation rate declined to 73% at last follow-up; unknown number of exclusions	Strengths ▪ Semiquantitative exposure measurement (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job code) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, NDI; cancers identified from National Cancer Statistics Clearing House (cancer registries)) ▪ Assessed disease incidence ▪ ≥5 years follow-up (mortality: 20 yrs; incidence: 21 yrs) Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for age, and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or occupational history ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sung *et al.* (2007)	Female electronics factory workers	T	P			Strengths ▪ Appropriate study and comparison groups ▪ No missing data Weaknesses ▪ Notable weakness in study population (i.e., majority of population <20 yrs old at first employment)	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment records from labor insurance database) ▪ Qualitative exposure estimate (i.e., ever employment at factory) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Taiwan National Cancer Registry) ▪ Assessed disease incidence ▪ 23 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age, and sex ▪ No missing data Weaknesses Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Tsai *et al.* (2007)	Male petroleum refinery and chemical workers, US			B		Strengths ▪ Appropriate study and comparison groups ▪ 0.87% loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company records, NDI, and SSA) ▪ 65 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics or other chemical exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, analyses by ≥10yrs of employment) Weaknesses ▪ No major weaknesses
Radican *et al.* (2008)	Aircraft maintenance employees	T				Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Unknown number of subjects excluded or lost to follow-up	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, facility files, walk-through surveys, and employee interviews) ▪ Amount of missing data unknown ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using a reliable source (*i.e.*, NDI/NDI Plus) ▪ 22 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ About 11% missing race (assumed white)	Strengths ▪ Exposure documented before outcome Weaknesses ▪ Insufficient consideration of latency (employment for at least 1-yr)

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Wilson *et al.* (2008)	Swedish general population	T	P			Strengths ▪ Appropriate study and comparison groups ▪ <2% excluded Weaknesses ▪ Amount lost to follow-up unknown	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported job titles from 1960 and 1970 National Population and Housing Censuses) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, CERIII) ▪ Assessed disease incidence ▪ 19 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age, sex, and smoking ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Did not consider relevant covariates in a time-varying manner (*i.e.*, smoking)	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Pukkala *et al.* (2009)	General population in Denmark, Finland, Iceland, Norway and Sweden	T	P			Strengths ▪ Appropriate study and comparison groups ▪ No exclusions Weaknesses ▪ Amount lost to follow-up unknown	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupation in censuses) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Unknown number of subjects with missing data ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using reliable sources (*i.e.*, Central Population Register and national registries) ▪ Assessed disease incidence ▪ 23-45 yrs of follow-up (depending on country) Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Calvert *et al.* (2011)	Dry cleaning workers		P			Strengths ▪ Appropriate study and comparison groups ▪ 5% loss to follow-up;< 1% excluded Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment at shops using PCE) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, unions, DMV, IRS, postal service, and NDI records) ▪ 65 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ No missing data Weaknesses ▪ Did not consider or control for: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (20 yrs since first employment; duration 5+ yrs) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Koh *et al.* (2011)	Male South Korean workers in a refinery and petrochemical complex			B		Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Unknown number of subjects lost to follow-up	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history, and department) ▪ Qualitative exposure estimate (*i.e.*, work history) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, Central Registry of Cancer in Korea) ▪ Deaths identified using a reliable source (*i.e.*, Korea National Statistical Office) ▪ Assessed disease incidence ▪ ≥5 years follow-up (mortality: 16 yrs; incidence: 9 yrs) Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, and sex ▪ No missing data Weaknesses ▪ Did not consider or control for: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or occupational history ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Lipworth *et al.* (2011)	Aircraft manufacturing workers	T	P			Strengths ▪ Appropriate sample and comparison groups ▪ <2% excluded; <2% lost to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, job codes/titles, facility files, walk-through visits, and employee interviews) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, CA Death Statistical Master File, NDI, SSA Death Master File, pension, other records, death certificates, and SSA Service to Epidemiologic Researchers and LexisNexis records) ▪ 49 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing race data unknown	Strengths ▪ Exposure documented before outcome Weaknesses ▪ Insufficient consideration of latency (1-yr lag)

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Seldén and Ahlborg Jr. (2010)	Dry cleaning workers in Sweden		P			Strengths ▪ Appropriate comparison group ▪ 2.8% loss to follow-up Weaknesses ▪ Low participation rate - 62.1% if companies that received a questionnaire did not respond	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employer reported job history) ▪ Qualitative exposure estimate (*i.e.*, employment in dry-cleaning/laundry) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using a reliable source (*i.e.*, national cancer registry) ▪ Assessed disease incidence ▪ 22 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (sensitivity analysis included 15-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove (2014b)	Marines & Navy Personnel at CL	T	P	B	V	Strengths ▪ Appropriate study and comparison groups ▪ <2% loss to follow-up Weaknesses ▪ Number of participants excluded unknown	Strengths ▪ Direct chemical exposure measurement (*i.e.*, measured in groundwater) ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data ▪ Assessed time-varying nature of exposure Weaknesses ▪ No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, commercial tracing service, and NDI) ▪ 30 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ Considered smoking using negative control diseases Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, 10-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2014a)	Civilian employees at CL and CP	T	P	B	V	Strengths ▪ Appropriate study and comparison groups ▪ ≤2% loss to follow-up Weaknesses ▪ Number of participants excluded unknown	Strengths ▪ Direct chemical exposure measurement (measured in groundwater, not used in the analysis) ▪ No missing data Weaknesses ▪ Qualitative exposure estimate (*i.e.*, employed at CL *vs* employed at CP) ▪ Did not assess time varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, a commercial tracing service, and NDI/NDI Plus) ▪ 30 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for or considered: age, sex, race, and occupation (as a proxy for other potential chemical exposures) ▪ Considered smoking using negative control diseases Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Did not include relevant covariates in a time-varying manner (*i.e.*, occupation) ▪ Amount of missing data is unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, 10-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Carreón *et al.* (2014)	Workers at a chemical manufacturing plant				V	Strengths ▪ Appropriate study and comparison groups ▪ 2% loss to follow-up ▪ <1% excluded Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment at facility) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, NDI, NDI Plus, and Florida Department of Health) ▪ 48 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race/ethnicity Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ 54.2% missing race/ethnicity; assumed white	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silver *et al.* (2014)	Microelectronics and business machine facility employees	T	P			Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ Relatively young cohort (mean age at hire was mid-20s, average follow-up 25.7 yrs) ▪ Amount excluded and lost to follow-up unknown	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment at facility and JEM) ▪ Missing, incomplete, and conflicting data regarding work dates, facility location, department, and position (particularly for early yrs) that are not addressed ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified using reliable sources (*i.e.*, SSA, NDI, IRS, and death certificates) ▪ 41 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race (in external analyses) Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures; race (in internal analyses) ▪ 16% missing race data (assumed white)	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (10-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Collins *et al.* (2015)	Benzene workers			B		Strengths ▪ Appropriate study and comparison groups ▪ <1% loss to follow-up Weaknesses ▪ Unknown number of exclusions	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment in three production areas at facility) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, HR records, NDI, state vital statistics bureaus) ▪ 70 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (15- and 30-yr lags) Weaknesses ▪ No major weaknesses
Linet *et al.* (2015)	NCI-CAPM cohort			B		Strengths ▪ Appropriate study and comparison groups ▪ <20% loss to follow-up (1.84%) or excluded (due to age ≤12 yrs, <1%) Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, factory records and job titles) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, factory records, medical records and death certificates) ▪ 28 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for age and sex Weaknesses ▪ Did not consider or control for: race/ethnicity (likely homogenous), prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other chemical co-exposures ▪ Did not include relevant covariates in a time-varying manner	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (10 yrs) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Buhagen *et al.* (2016)	Train repair and maintenance workers	T				Strengths ▪ Appropriate study and comparison groups ▪ <5% excluded Weaknesses ▪ Amount lost to follow-up unknown	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, employment at workshop) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases and deaths identified using reliable sources (*i.e.*, Norwegian Cancer Registry and Statistics Norway) ▪ Assessed disease incidence ▪ 51 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency
Mundt *et al.* (2017)	VC or PVC resin manufacturing workers				V	Strengths ▪ Appropriate study and comparison groups ▪ <2% excluded; <3% loss to follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure assessment (*i.e.*, employment at factory >1 yr) ▪ Qualitative exposure estimate (*i.e.*, any exposure) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, SSA, NDI, and death certificates) ▪ 72 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age and sex ▪ No missing data Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
ATSDR (2018a)	Marines & Navy personnel and civilian employees at CL and CP	T	P	B	V	Strengths ▪ Appropriate study and comparison groups Weaknesses ▪ 70% of CL Marines, 72% CP Marines, 55% CL civilians and 62% CP civilians did not enroll ▪ 10% of those who reported an outcome excluded for not completing HIPAA form	Strengths ▪ Direct chemical exposure measurement (*i.e.*, measured in groundwater) ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data ▪ Assessed time-varying nature of exposure Weaknesses ▪ No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	Strengths ▪ Deaths validated using reliable sources (*i.e.*, medical records and death certificates) ▪ Assessed disease incidence ▪ 41 yrs of follow-up Weaknesses ▪ Initial case identification relied on self-report	Strengths ▪ Controlled for or considered: age, sex, race, smoking, alcohol consumption, and other potential occupational/chemical exposures Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Did not consider relevant covariates in a time-varying manner (*i.e.*, smoking, alcohol consumption, occupational exposures) ▪ >5% missing data for smoking, alcohol, and other occupational exposures	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, "virtually all" participants developed cancer ≥10 yrs after being stationed or employed at CL) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Callahan *et al.* (2019)	Dry-cleaning union members in St. Louis, MO		P			Strengths ▪ Appropriate study and comparison groups ▪ About 7% excluded Weaknesses ▪ Amount lost to follow-up unknown	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, monitoring studies of the dry-cleaning industry applied to job titles from union records) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Deaths identified using reliable sources (*i.e.*, union records, SSA, DMV, credit bureaus, state bureaus of social services, telephone and street directories, NDI, death certificates) ▪ 67 yrs of follow-up Weaknesses • Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race Weaknesses ▪ Did not consider or control for: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (10- and 20-yr lag) Weaknesses ▪ No major weaknesses

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Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2024b)	Marines & Navy personnel and civilian workers at CL and CP	T	P	B	V	Strengths ▪ Appropriate study and comparison groups ▪ <2% excluded Weaknesses ▪ Unknown loss to follow-up	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, assignment or employment at base) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers, NDI, and cancer registries) ▪ Assessed disease incidence ▪ 22 yrs of follow-up Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race, and (for civilians) blue-collar work as a proxy for other occupational exposures Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or (for Marines & Navy) other potential occupational exposures ▪ 5.2% of CP Marines & Navy personnel and 14.7% of CP civilians had other/unknown race	Strengths ▪ Exposure documented before outcome ▪ Appropriate consideration of latency (*i.e.*, follow-up began 10 yrs after last exposure of interest) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2024a)	Marines & Navy personnel and civilian workers at CL and CP	T	P	B	V	Strengths ▪ Appropriate study and comparison groups ▪ <1% loss to follow-up ▪ No exclusions Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, assignment or employment at base) ▪ Did not assess time-varying nature of exposure	Strengths ▪ Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers and NDI) ▪ 40 yrs of follow-up Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, race, and (for civilians) blue-collar work (proxy for other exposures) Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or, for marines/navy, other potential occupational exposures ▪ 5.2% of CP Marines/ Navy personnel and 14.7% of CP civilians had other/unknown race	Strengths ▪ Exposure documented before outcome Weaknesses ▪ No consideration of latency (though, 75% of the deaths occurred >10 yrs after end of water contamination)
						▪	▪	▪	▪	▪

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Case-Control										
Schoenberg *et al.* (1984)	White, male residents of NJ	T	P			Strengths ▪ Appropriate case and control selection ▪ 89.7 and 86.6% enrollment rates in cases and controls, respectively Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Qualitative exposure estimate (*i.e.*, occupation) ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths ▪ Cases identified using reliable sources (*i.e.*, SEER Network and NJ Cancer Registry) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age, sex, race/ethnicity, smoking, chronic bladder inflammation and family history ▪ No missing data Weaknesses ▪ Did not control for or consider: prior cancer treatment, genetics, or other potential occupational exposures	Strengths ▪ Exposure considered prior to diagnosis Weaknesses ▪ No consideration of latency
Smith *et al.* (1985)	NCI National Bladder Study		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ Unknown response rates	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, NCI SEER) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking Weaknesses ▪ Did not control for race, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Exposure considered prior to diagnosis ▪ Appropriate consideration of latency (*i.e.* analyses with 10+ yrs duration of employment – not shown) Weaknesses ▪ No major weaknesses ▪

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silverman *et al.* (1989a)	White men in the NCI National Bladder Study		P			Strengths ▪ Appropriate case and control selection ▪ 84% enrollment rate in controls Weaknesses ▪ 75% response rates in cases	Strengths ▪ No major strengths Weaknesses ▪ Qualitative exposure estimate (*i.e.*, occupation/industry title) ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and grouped by occupational code and by potential to similar exposures) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, NCI SEER) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race, geographic area, and smoking Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time at or after diagnosis ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silverman *et al.* (1989b)	Non-white men in the NCI National Bladder Study		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ Unknown participation rates	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and grouped by occupational code and by potential to similar exposures) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, NCI SEER) and histologically confirmed ▪ Assessed disease incidence Weaknesses • No major weaknesses	Strengths ▪ Controlled for: age, sex, geographic area, smoking, employment in other high-risk occupations Weaknesses • Did not control for or consider: race/ethnicity, for prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Appropriate consideration of latency (*i.e.*, analyses by 5+ yrs duration of employment) Weaknesses ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silverman *et al.* (1990)	White women in the NCI National Bladder Study		P			Strengths ▪ Appropriate case and control selection ▪ 81% participation rate in controls Weaknesses ▪ 69% participation rate in cases	Strengths ▪ Semiquantitative exposure estimates (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and grouped by occupational code and by potential to similar exposures) ▪ Amount of missing data unknown	Strengths ▪ Cases identified using a reliable source (*i.e.*, NCI SEER) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race, geographic area, and smoking Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ Appropriate consideration of latency (*i.e.*, analyses with 5+ yrs duration of employment) Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪
Steineck *et al.* (1990)	Swedish male general population		P	B		Strengths ▪ Appropriate case-control selection groups ▪ 80% participation rate in cases Weaknesses ▪ 79% participation rates among controls	Strengths ▪ Semiquantitative exposure estimate (considered duration, frequency, and intensity) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis	Strengths ▪ Cases identified using reliable sources (*i.e.*, cancer registry and urological departments) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking Weaknesses ▪ Did not consider or control for: race/ethnicity, (prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Appropriate consideration of latency (4-yr lag) Weaknesses ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Burns and Swanson (1991)	Residents of the Detroit metropolitan area who participate in the Occupational Cancer Incidence Surveillance Study (OCISS)		P			Strengths ▪ Appropriate case selection ▪ 94% and 95% participation rates in cases and controls, respectively Weaknesses ▪ Inappropriate control selection (*i.e.*, cancer controls)	Strengths ▪ Only about 1% missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupation or industry held for longest time period) ▪ Qualitative exposure estimate (*i.e.*, occupation/industry title) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using reliable sources (*i.e.*, local SEER registry and Metropolitan Detroit Cancer Surveillance System) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race, and smoking Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetic factors, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Aschengrau *et al.* (1993)	Residents of five Upper Cape towns, MA		P			Strengths ▪ Appropriate case and control selection ▪ 83% participation rate in cases ▪ Characteristics of participants and non-participants were similar Weaknesses ▪ 74% participation rate in controls	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered intensity) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, exposure modelled based on subjects' residences on streets with vinyl-lined/asbestos cement pipes) ▪ Amount of missing data unknown	Strengths ▪ Cases identified using reliable sources (*i.e.*, Massachusetts Cancer Registry and confirmed by medical professional) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, occupational exposure to PCE, benzene, and other solvents, smoking, and history of a cancer-associated job Weaknesses ▪ Did not consider or control for: race/ethnicity (though majority White), prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Amount of missing data unknown	Strengths ▪ Exposure considered prior to diagnosis ▪ Appropriate consideration of latency (15-yr lag) Weaknesses ▪ No major weaknesses
Greenland *et al.* (1994)	Workers at a transformer-assembly facility	T		B		Strengths ▪ Appropriate case and control selection Weaknesses ▪ About 40% of potential study population excluded (36% missing job history)	Strengths ▪ <2% of person-yrs missing exposure level, assigned by imputation Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history records and JEM) ▪ Qualitative exposure estimate (*i.e.*, any exposure)	Strengths ▪ Deaths identified using reliable sources (*i.e.*, company pension office and death certificates); subset of cancer diagnoses were validated by medical professional Weaknesses ▪ Assessed mortality only	Strengths ▪ Controlled for: age, sex, and race ▪ No missing data Weaknesses ▪ Did not control for or consider: smoking, prior cancer treatment, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Exposure considered prior to death Weaknesses ▪ Insufficient consideration of latency (2-yr lag)

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Siemiatycki *et al.* (1994)	Male residents of Montreal, Quebec, Canada	T	P			Strengths ▪ Appropriate case selection ▪ 84% participation rate in cases Weaknesses ▪ Inappropriate control selection (*i.e.*, cancer controls) ▪ 72% response rates in controls	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, hospital records) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, ethnicity, and smoking Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ Appropriate consideration of latency (5-yr lag) Weaknesses ▪ Unclear if exposure period included time after diagnosis
Swanson and Burns (1995)	Females in the Detroit Metropolitan Area, MI		P			Strengths ▪ Appropriate case and control selection ▪ 96% and 98.6% participation rate in cases and controls, respectively Weaknesses ▪ No major weaknesses	Strengths ▪ No major strengths Weaknesses ▪ Indirect exposure measurement (*i.e.*, self-reported occupational history and proxies for cases and controls unable to respond) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, Metropolitan Detroit Cancer Surveillance System) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race, and smoking Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ No major strengths Weaknesses ▪ No consideration of latency ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Teschke *et al.* (1997)	British Columbia general population		P			Strengths ▪ Appropriate case and control selection ▪ 88.2% and 80.3% enrollment rate in cases and controls, respectively Weaknesses ▪ No major weaknesses	Strengths ▪ No missing data Weaknesses ▪ Indirect exposure measurement (*i.e.*, self-reported occupational history and proxies for cases and controls unable to respond) ▪ Qualitative exposure estimate (*i.e.*, based on occupational group) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, British Columbia Cancer Agency) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age, sex, smoking, history of bladder infections, prior cancer, or other occupational and non-occupational exposures Weaknesses ▪ Did not consider or control for: race/ethnicity or genetics ▪ Amount of missing data unknown	Strengths ▪ Appropriate consideration of latency (5-, 10- and 15-yr lags) Weaknesses ▪ Unclear if exposure period included time after diagnosis
Gérin *et al.* (1998)	Canadian white males			B		Strengths ▪ Appropriate case selection ▪ 82% participation rate in cases Weaknesses ▪ Inappropriate control selection (*i.e.*, non-compulsory electoral lists) ▪ 71% participation rate in controls ▪ Case and control participation rates differed	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and expert opinion) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, medical records); vital status for controls confirmed *via* interview ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for or considered: age, sex, ethnicity, smoking, and co-exposures (toluene, xylene, styrene, and aromatic amines) Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Amount of missing data unknown	Strengths ▪ Exposure considered prior to diagnosis Weaknesses ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Pesch *et al.* (2000)	General population in five German regions	T	P	B		Strengths ▪ Appropriate case and control selection ▪ 84% participation rate in cases Weaknesses ▪ 71% participation rate in controls	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history, JEM, and JTEM) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, hospital records) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking Weaknesses ▪ Did not control for or consider: race, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Zheng *et al.* (2002)	Iowa general population		P			Strengths ▪ Appropriate case and control selection ▪ 85% and ≥80 participation rates in cases and controls, respectively ▪ Weaknesses ▪ No major weaknesses	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, state cancer registry) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, smoking, and family history of bladder cancer Weaknesses ▪ Did not control for or consider: race/ethnicity, prior cancer treatment, personal history of bladder cancer, chronic bladder inflammation, genetics, or other potential occupational exposures ▪ >5% of men missing data for family history of bladder cancer	Strengths ▪ Appropriate consideration of latency (*i.e.*, analyses by 10+ years of exposure) Weaknesses ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Colt *et al.* (2004)	NH general population		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ 74% and 67% participation rates in cases and controls, respectively	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Qualitative exposure estimate (*i.e.*, based on occupation) ▪ Amount of missing data unknown ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, NH State Cancer Registry) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking status Weaknesses ▪ Did not control for or consider: race, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data unknown	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ Not consideration of latency
Gaertner *et al.* (2004)	General populations of seven Canadian provinces		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ 66% and 77% participation rates in male female cases, respectively, and 59% and 65% in male and female controls, respectively ▪ Case and control participation rates differed ▪ Inappropriate exclusion of native Canadians and military personnel	Strengths ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Qualitative exposure estimate (*i.e.*, based on occupation) ▪ Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths ▪ Cases identified using reliable sources (*i.e.*, provincial cancer registries) and were histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race/ethnicity, and smoking ▪ No missing data Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Lynge *et al.* (2006)	Laundry and dry-cleaning workers in Denmark, Finland, Norway, and Sweden		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ Low participation rates for interviews: Norway (57% of eligible cases and 64% of eligible controls); Sweden (63% of eligible cases and 60% of eligible controls); missing pension scheme data (Denmark 9% and Finland 25%) ▪ Case and control participation rates differed	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self- or next of kin-reported census data, interviews [Finland, Norway and Sweden], pension data [Denmark and Finland], and industry and telephone books [Denmark]) ▪ Unclassifiable exposure records (Finland 41%, and Sweden 35%) ▪ Potential for recall bias (*i.e.*, interviews conducted after diagnosis)	Strengths ▪ Cases identified using reliable sources (*i.e.*, national population, death and cancer registries) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking Weaknesses ▪ Did not control for or consider: race/ethnicity, prior cancer treatment, chronic bladder inflammation, personal or family history if bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure considered prior to diagnosis ▪ Appropriate consideration of latency (*i.e.*, analyses by 5+ years of employment) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Reulen *et al.* (2007)	Residents of Limburg, Belgium	T	P			Strengths ▪ Appropriate case-control selection groups ▪ 90.9% participation rate in cases Weaknesses ▪ 74% participation rate in controls ▪ Case and control participation rates differed	Strengths ▪ No major strengths Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Qualitative exposure estimate (*i.e.*, job title) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, Limburg Cancer Registry) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and smoking Weaknesses ▪ Did not control for or consider: race/ethnicity, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ No consideration of latency

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Dryson *et al.* (2008)	New Zealand general population		P			Strengths ▪ Appropriate case selection Weaknesses ▪ Low participation rates in cases (~64%) and controls (~48%) ▪ Case and control participation rates differed; those who participated systematically differed from those who did not (older subjects and certain occupational classes were more likely to participate) ▪ Inappropriate comparison group (*i.e.*, non-compulsory electoral roll)	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration [in sensitivity analyses]) ▪ <1% missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, New Zealand Cancer Registry) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, ethnicity, and smoking ▪ <1% missing data Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupation exposures	Strengths Appropriate consideration of latency (*i.e.*, sensitivity analyses include 10+ yrs of exposure) Weaknesses ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Colt *et al.* (2011)	General population of NH, VT, and ME		P			Strengths ▪ Appropriate case and control selection Weaknesses ▪ 65% response rates in cases and controls	Strengths ▪ <2% missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) ▪ Qualitative exposure estimate (*i.e.*, job title and industry ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using reliable sources (*i.e.*, hospital pathology departments, hospital cancer registries, and state cancer registries) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, race/ethnicity, smoking status, and employment in other high-risk occupations ▪ <2% missing data Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics	Strengths ▪ No major strengths Weaknesses ▪ Unclear if exposure period included time after diagnosis ▪ No consideration of latency
Christensen *et al.* (2013)	Male Canadian citizens residents of Montreal	T	P			Strengths ▪ Appropriate case selection ▪ 82% case participation rate Weaknesses ▪ Inappropriate control selection (non-compulsory electoral lists) ▪ 72% control participation rate	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and expert opinion) ▪ Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths ▪ Cases identified using a reliable source (*i.e.*, hospital records) and histologically confirmed ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, ethnicity, smoking, and aromatic amines exposure Weaknesses ▪ Did not control for or consider: prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics ▪ Amount of missing data is unknown	Strengths ▪ Appropriate consideration of latency (5-yr lag) Weaknesses ▪ Unclear if exposure period included time after diagnosis

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Hadkhale *et al.* (2017)	General population of Finland, Iceland, Norway, and Sweden	T	P	B		Strengths ▪ No major strengths Weaknesses ▪ Inappropriate case and control selection (cases and controls could have a prior history of cancer)	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, self-reported occupational history in decennial censuses and JEM)	Strengths ▪ Cases identified using reliable sources (*i.e.*, national cancer registries) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for: age, sex, and other potential exposures (*i.e.*, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust, and sulfur dioxide) Weaknesses ▪ Did not control for or consider: race/ethnicity, smoking, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, genetics, or other potential occupational exposures ▪ Amount of missing data is unknown	Strengths ▪ Exposure considered prior to diagnosis ▪ Appropriate consideration of latency (10-yr lag) Weaknesses ▪ No major weaknesses

Citation	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Shala *et al.* (2023)	Offshore petroleum workers in Norway			B		Strengths ▪ Appropriate case-control selection groups Weaknesses ▪ Low participation rate among controls (31% of eligible workers did not participate); few exclusions for missing information (<2%) ▪ No information on how those who did not participate differed from those who did	Strengths ▪ Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) ▪ No missing data Weaknesses ▪ Indirect chemical exposure measurement (*i.e.*, work history, job codes, and JEM)	Strengths ▪ Cases were identified using a reliable source (*i.e.*, Cancer Registry of Norway) ▪ Assessed disease incidence Weaknesses ▪ No major weaknesses	Strengths ▪ Controlled for age, sex, smoking, and PAHs ▪ ≤5% missing data; addressed missing data with multiple imputation Weaknesses ▪ Did not consider or control for: race/ethnicity, prior cancer treatment, chronic bladder inflammation, personal or family history of bladder cancer, or genetics,	Strengths ▪ Exposure considered prior to diagnosis ▪ Appropriate consideration of latency (10-,15-, and 20-yr lags) Weaknesses ▪ No major weaknesses

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Benzene; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; DMV = Department of Motor Vehicles; FIOH = Finnish Institute of Occupational Health; HCFA = Health Care Financing Administration; HR = Hazard Ratio; IRS = Internal Revenue Service; JEM = Job-Exposure Matrix; JTEM = Job-Task-Exposure Matrix; MA = Massachusetts; ME = Maine; MI = Michigan; NCI = National Cancer Institute; NCI-CAPM = National Cancer Institute-Chinese Academy of Preventive Medicine; NDI = National Death Index; NH = New Hampshire; NJ = New Jersey; P = Perchloroethylene; PCE = Perchloroethylene; PVC = Polyvinyl Chloride; RR = Relative Risk; SEER = Surveillance, Epidemiology, and End Results; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SSA = Social Security Administration; T = Trichloroethylene; TCE = Trichloroethylene; U-TCA = Urinary Trichloroacetic Acid; US = United States; USPS = United States Postal Service; VA= Veterans Administration; VC = Vinyl Chloride; VT = Vermont; Yrs = Years.

Attachment D

TCE Epidemiology Studies

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Table D.5 TCE and Bladder Cancer Meta-analyses and Pooled Study Results

Table D.1 TCE and Bladder Cancer Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Garabrant *et al.* (1988)	US	Aircraft manufacturing workers	B	–	14,067	1958-1982	Personnel records	Mort	Bladder and other urinary organs	SSA, California DMV, credit records, death certificates, California Death Tapes	1958-1982
Shannon *et al.* (1988)	Canada	Lamp manufacturing workers	M	–	826	1960-1975	Job titles	Mort	Bladder	Ontario Cancer Treatment and Research Foundation cancer registry	1964-1982
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Bladder	Death certificate	1942-1980
Costa *et al.* (1989)	Italy	Aircraft manufacturing workers	B	–	7,105	1954-1981	Job titles	Mort	Urinary system	Death certificate	1954-1981
Sinks *et al.* (1992)	US	Paperboard Printing Workers	B	19-83	2,050	1957-1988	Work history and Material Safety Data Sheets	Inc & Mort	Bladder	SSA (mortality) and SEER registry (morbidity)	1957-1988
Axelson *et al.* (1994) [Axelson *et al.* 1978; 1984]	Sweden	TCE-exposed workers	M	<80	1,421	1955-1979	U-TCA	Inc	Bladder	Swedish cause of death and cancer registers	1955-1986 mortality, 1958-1987 cancer
Anttila *et al.* (1995)	Finland	FIOH workers	B	–	3,089	1965-1982	U-TCA	Inc	Bladder, ureter, and urethra	Finnish Cancer Registry and Central Statistical Office of Finland	1967-1992

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Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Morgan *et al.* (1998)	US	Aircraft manufacturing workers	B	–	20,508 TCE sub-cohort: 4,733	1950-1985	JEM	Mort	Bladder	SSA and NDI	1950-1993
Ritz (1999)	US	Uranium-processing workers	M	30.5[a]	3,814	1951-1989	JEM	Mort	Bladder	SSA and NDI	1951-1989
Hansen *et al.* (2001)	Denmark	TCE exposed workers	B	–	803	1964-1989	U-TCA & air-TCE	Inc	Bladder	Danish Cancer Registry	1968-1996
Travier *et al.* (2002)	Sweden	Dry-cleaning workers	B	–	3,742	1960/1970 census	Census JEM	Inc	Bladder	CERIII	1971-1989
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	39.25[b]	86,868	1973-1997	Employment in the factory	Mort	Bladder	National Mortality Database	1985-1997
Raaschou-Nielsen *et al.* (2003)	Denmark	Blue-collar workers at TCE using companies	B	–	40,049	1964-1997	Employed at TCE-using companies and JEM	Inc	Bladder	Danish cancer registry	1968-1997
Zhao *et al.* (2005)	US	Aerospace workers	M	Mortality: 68.7[b] Incidence: 68.6[b]	Mortality: 6,044 Incidence: 5,049	1950-1993	JEM	Inc & Mort	Bladder	SSA, vital statistics, NDI, state cancer registries	Mortality:1950-2001 Incidence: 1988-2000
Boice *et al.* (2006)	US	Aerospace workers	M	–	8,372	1948-1999	JEM	Mort	Bladder	California death tapes, NDI, death certificates	1948-1999
Sung *et al.* (2007)	Taiwan	Electronics factory workers	F	–	63,982	1973-1992	Employment records from labor insurance database	Inc	Bladder	Taiwan National Cancer Registry	1979-2001

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Radican *et al.* (2008) [Blair *et al.*, 1998; Spirtas *et al.*, 1991]	US	Aircraft maintenance employees	B	–	14,455	1952-1956	JEM	Mort	Bladder	NDI Plus	1979-2000
Wilson *et al.* (2008)	Sweden	Employed Swedish residents	B	–	4,197,684	1960/1970 census	Industry/occupation based on census	Inc	Bladder	CERIII	1971-1989
Pukkala *et al.* (2009) [Lynge and Thygesen, 1990; Andersen *et al.*, 1999; Ji *et al.*, 2005]	Denmark, Finland, Iceland, Norway, and Sweden	General population	B	30-64[c]	~ 14.9 million	1960-1990	Occupation based on first census at age 30-64: Denmark: 1970 Sweden: 1960, 1970, 1980, 1990 Norway: 1960, 1970, 1980 Finland: 1970, 1980, 1990 Iceland: 1981	Inc	Bladder, ureter, and urethra	National registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	45,318 (5,443 exposed to TCE)	–	JEM	Mort	Bladder and other urinary organs	California Death Statistical Master File, NDI, SSA, death certificates, and company records	1960-2008
Bove *et al.* (2014b)	US	Marines & Navy personnel at CL and CP	B	CL & CP: 20-49[d]	CL: 154,932, CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Bladder	SSA and NDI	1979-2008

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Silver *et al.* (2014)	US	Microelectronics facility workers	B	25.7-28.7[a]	34,494	1969-2001	Employment at the facility	Mort	Bladder and other urinary organs	SSA, NDI, IRS, and death certificates	1969-2009
Buhagen *et al.* (2016)	Norway	Train repair and maintenance workers	M	–	997	1954 to mid-1990s	Employment at the facility	Inc	Urinary bladder	Norwegian cancer registry	1960-2010
ATSDR (2018a)[e]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[f] Civilian Employees CL: 60-64[f] CP: ≥65[f]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168, CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines & Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Bladder	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel: 1975-2012 Civilian Employees: 1972-2012

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; FIOH = Finnish Institute of Occupational Health; Inc = Incidence; IRS = Internal Revenue Service; JEM = Job-Exposure Matrix; M = Males; Mort = Mortality; NDI = National Death Index; SEER = Surveillance, Epidemiology, and End Results; SSA = Social Security Administration; U-TCA = Urinary Trichloroacetic Acid; US = United States; Yr = Year.
$\bar{x}$ = Mean;– = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Mean age at hire. Ritz (1999); Silver *et al.* (2014)
(b) Mean age at end of follow-up. Chang *et al.* (2003); Zhao *et al.* (2005)
(c) Age at initial census. Pukkala *et al.* (2009)
(d) Median age from start to end of follow-up. (Bove *et al.*, 2014b).
(e) Ages and population sizes are reflective of Marines, Navy, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis. (ATSDR, 2018a).
(f) Median age at survey or death. (ATSDR, 2018a).

Table D.2 TCE and Bladder Cancer Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Garabrant *et al.* (1988)	US national population	Mort	SMR	Overall	17	13.44	1.26 (0.74-2.03)	–	Age, sex, race, and calendar year
				Duration of Employment (Yrs)[b]					
				4-5	0	0.74	0 (–)	–	
				5-9	4	3.79	1.05 (–)		
				10-14	5	3.51	1.42 (–)		
				15-19	5	2.62	1.91 (–)		
				20-24	0	1.63	0 (–)		
				25-29	2	0.76	2.66 (–)		
				30+	1	0.41	2.45 (–)		
Shannon *et al.* (1988)	Non-coiling and wire-drawing area workers	Mort	SMbR	Coiling and wire-drawing area workers	3	3.22	0.93 (0.19-2.72)	–	Age, sex, and calendar period
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	2	4	0.5 (0.06-1.79)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	0.9 (0.18-2.62)		
Costa *et al.* (1989)	Italy general population	Mort	SMR	Male blue-collar workers and technical staff	7	–	0.74 (0.30-1.53)	–	Age and sex
				Female blue-collar workers and technical staff	–		–		
				Males					
				Hired ≤1954	3	–	0.43 (0.09-1.27)	–	
				Hired >1954	4		1.55 (0.42-3.97)		
				Males hired ≤ 1954, Duration of Employment					
				0-4 yrs	–	–	–	–	
				5-14 yrs	–		–		
				≥15 yrs	3		0.48		
				Males hired > 1954, Duration of Employment					
				0-4 yrs	1	–	2.17	–	
				5-14 yrs	1		2.13		
				≥15 yrs	1		1.61		
Sinks *et al.* (1992)	US general population	Mort	SMR	Overall	1	0.4	2.6 (0.1-14.7)	–	Age, sex, and calendar period

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
	Atlanta-SEER registry (1973-1977)	Inc	SIR	All white male employees	3	2.8	1.1 (0.2-3.1)	–	Age
Axelson *et al.* (1994)	Sweden general population	Inc	SIR	Overall	8	7.9	1.02 (0.44-2.52)	–	Age, and calendar yr
Anttila *et al.* (1995)	Finland general population	Inc	SIR	Overall	5	–	0.82 (0.27-1.90)	–	Sex, age, and calendar yr
				FIOH Workers, Yrs of Follow-up					
				0-9 yrs	1	–	0.65 (0.02-3.59)	–	
				10-19 yrs	2		0.61 (0.07-2.22)		
				20+ yrs	2		1.51 (0.18-5.44)		
Morgan *et al.* (1998)	US general population	Mort	SMR	Overall cohort	23	27.3	0.84 (0.53-1.26)	–	–
				TCE-Exposed Sub-cohort					
				Overall	8	5.9	1.36 (0.59-2.68)	–	
				Low exposure	1	1.97	0.51 (0.01-2.83)		
				High exposure	7	3.90	1.79 (0.72-3.69)		
	Low and no exposed		RR	Peak: medium & high exposure	5	–	1.41 (0.52-3.81)		Age and sex
	Unexposed			Cumulative (low)	1	–	0.69 (0.09-5.36)		
				Cumulative (high)	7	–	**2.71 (1.10-6.65)**		
Ritz (1999)	US general population	Mort	SMR	Overall	8	6.83	1.17 (0.50-2.31)	–	Age, and calendar yr
Hansen *et al.* (2001)	Danish general population	Inc	SIR	Men	10	9.4	1.1 (0.5-2.0)	–	Age, sex, and calendar yr
				Women	0	0.5	–		
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**People Classified With Relevant Occupational or Industrial Code on ≥1 Census**					Sex, age, calendar period, geographic region, and urban setting
				Overall	145	–	1.01 (0.86-1.19)	–	
				People Classified With Relevant Occupational or Industrial Code on Both Censuses					
				Overall	16	–	1.00 (0.61-1.63)	–	
				Female	4	–	0.59 (0.22-1.57)	0.13	
				Male	12	–	1.32 (0.75-2.32)		
Chang *et al.* (2003)	Taiwan general population	Mort	SMR	Male	1	1.04	0.96 (0.01-5.36)	–	Age, calendar yr, and sex
				Female	1	1.04	0.96 (0.01-5.33)		
Raaschou-	Danish general	Inc	SIR	Men	203	197.6	1.0 (0.89-1.18)	–	Sex, age, and

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Nielsen *et al.* (2003)	population			Women	17	10.6	1.16 (0.93-2.57)		calendar yr
Zhao *et al.* (2005)	Low TCE exposure group	**Cumulative TCE Exposure**							Time since first employment, SES, age at event, and other measured carcinogens (*i.e.*, hydrazine, PAHs, mineral oils)
		No exposure lag							
		Mort	RR	Low TCE exposure	8	–	Ref.	0.572	
				Medium TCE exposure	6		0.63 (0.10-3.97)		
				High TCE exposure	3		1.58 (0.13-18.8)		
		Inc	RR	Low TCE exposure	20		1.00	**0.048**	
				Medium TCE exposure	19		1.79 (0.62-5.17)		
				High TCE exposure	11		3.80 (0.97-14.8)		
		20-yr exposure lag							
		Mort	RR	Low TCE exposure	8	–	Ref.	0.533	
				Medium TCE exposure	7		0.95 (0.15-6.02)		
				High TCE exposure	2		1.85 (0.12-27.7)		
		Inc	RR	Low TCE exposure	20		Ref.	0.064	
				Medium TCE exposure	20		1.76 (0.61-5.10)		
				High TCE exposure	10		3.68 (0.87-15.5)		
Boice *et al.* (2006)	California general population	Mort	SMR	Overall	5	4.4	–	–	Race, sex, age, and calendar yr of death
				Test Stand Mechanics (Male)	5	3.0	1.66 (0.54-3.87)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Sung *et al.* (2007)	Taiwanese general population	Inc	SIR	All female workers	3	8.8	0.34 (0.07-1.00)	–	Age and calendar yr
Radican *et al.* (2008)	Unexposed workers	Mort	HR	Overall	25	–	0.80 (0.41-1.58)	–	Age, sex, race, and calendar time
				Cumulative TCE Exposure Score					
				Males					
				Low, intermittent	17	–	1.03 (0.44-2.41)	–	
				Low, continuous	14		1.32 (0.55-3.18)		
				Peak, infrequent	2		0.59 (0.12-2.78)		
				Peak, frequent	8		0.82 (0.30-2.19)		
				Females					
				Low, intermittent	0	–	–	–	
				Low, continuous	0				
				Peak, infrequent	0				
				Peak, frequent	1		0.36 (0.04-3.02)		
Wilson *et al.* (2008)	Total employed population	Inc	SIR	**Machine and Electronics Industry**					Age, sex, and calendar yr
				Female	106	–	1.22 (1.00-1.48)	–	
				Male	1,740		**1.13 (1.08-1.18)**		
				Occupation					
				Shop and construction metal work					
				Female	52	–	1.30 (0.97-1.70)	–	
				Male	2,193		**1.10 (1.06-1.15)**		
				Machine assembly					
				Male	214	–	**1.27 (1.11-1.45)**	–	
				Metal platers					
				Female	3	–	4.05 (0.81-11.82)	–	
				Metal plating work					
				Male	2	–	0.97 (0.62-1.44)	–	
				Shop and metal industry work					
				Female	34	–	1.36 (0.94-1.89)	–	
				Male	284		**1.18 (1.05-1.33)**		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Pukkala *et al.* (2009)	Employed population in Denmark, Finland, Iceland, Norway, and Sweden	Inc	SIR	**Men**					Country, sex, age, and 5-yr calendar periods
				Mechanics	8138	–	**1.11 (1.08-1.13)**	–	
				Electrical Workers	2758		**1.09 (1.05-1.13)**		
				Painters	1642		**1.08 (1.03-1.14)**		
				Printers	1018		**1.19 (1.12-1.27)**		
				Women					
				Mechanics	180	–	**1.21 (1.04-1.40)**	–	
				Electrical Workers	123		1.05 (0.88-1.26)		
				Painters	15		1.52 (0.85-2.51)		
				Printers	126		**1.46 (1.22-1.74)**		
Lipworth *et al.* (2011)	California general population (white workers), US general population (non-white workers)	Mort	SMR	Factory workers exposed to TCE	35	34	1.03 (0.72–1.43)	–	Race, age, calendar yr, and sex
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-3,100)[b]	4	–	0.81 (0.26-2.50)	–	
				Medium/high (>3,100-8,585)[b]	7		0.84 (0.34-2.10)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[c]			Low (>1-3,100)	0		0.00		
				Medium (>3,100-7,700)	5		2.69 (0.63-11.46)		
				High (>7,700-39,745)	2		0.92 (0.15-5.55)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Silver *et al.* (2014)	Controls[d]	Mort	HR	Cumulative TCE exposure	–	–	0.04 (0.00-5.71)	–	Pay code, age, and sex
	US general population plus New York State (without NYC)		SMR	**Hourly Employees**					Age, sex, calendar period, and pay code
				Males	32	–	1.02 (0.70-1.44)	–	
				Females	13		0.63 (0.34-1.09)		
				Salaried Employees					
				Males	3	–	0.81 (0.17-2.36)	–	
				Females	0		0.00 (0.00-14.3)		
Buhagen *et al.* (2016)	Norway general population	Inc	SIR	Overall	11	15.5	0.7 (0.4-1.3)	–	Age, sex, and calendar yr
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[e,f]					
				Low (<110)	88	–	1.28 (0.76-2.15)	–	
				Medium (110-<11,030)	83		1.68 (1.00-2.82)		
				High (≥11,030)	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)			Medium (110-<11,030)	83		1.34 (0.98-1.85)		
				High (≥11,030)	11		0.74 (0.39-1.43)		
	CP civilian employees			**CL Civilian Employees**					None
				Cumulative exposure level (µg/L-mos)[e,g]					
				Low (<10,868)	8	–	1.02 (0.41-2.54)	–	
				Medium (10,868-<50,563)	2		0.32 (0.07-1.45)		
				High (≥50,563)	3		1.81 (0.50-6.53)		
	CL civilian employees with low exposure (<10,868 µg/L-mos)			Medium (10,868-<50,563)	2		0.32 (0.07-1.50)		
				High (≥50,563)	3		1.78 (0.47-6.77)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; NYC = New York City; OR = Odds Ratio; PAHs = Polycyclic Aromatic Hydrocarbons; PCE = Tetrachloroethylene; Ref. = Reference; RR = Relative Risk; SEER = Surveillance, Epidemiology,

and End Results; SES = Socioeconomic Status; SIR = Standardized Incidence Ratio; SMbR = Standardized Morbidity Ratio; SMR = Standardized Mortality Ratio; TVOC = Total Volatile Organic Compound; µg/L = Micrograms per Liter; US = United States; VC = Vinyl Chloride; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
Studies shown in square brackets previously examined this association in this population.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Garabrant *et al*. (1988) did not report CIs, but stated that none of the SMRs for duration of employment were statistically significant and that there was no significant trend. They also evaluated risk in 5 year increments of year of death and similarly reported no statistically significant risks in any period and no significant trend.
(b) Exposure groups are unclear in Bove *et al*. (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.
(c) To evaluate exposure-response relationships, Bove *et al*. (2014b) evaluated continuous and $\log^{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(d) Silver *et al*. (2014) stated, "The cases' cumulative chemical exposure scores were compared to those of other members of the full riskset (herein referred to as 'controls') who started work at the facility at an age which was less than the case's age at death and who survived longer than the case."
(e) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (3,948 µg/L-mos) and 90th (7,863 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018a).
(f) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018a).
(g) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018a).

Table D.3 TCE and Bladder Cancer Case-Control Study Characteristics

Study	Location	Outcome Type	Cancer Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (yrs)	Cases		Controls		
							N	Source	N	Source	
Schoenberg *et al.* (1984)	US	Inc	Urinary bladder or papilloma not specified as benign	1978-1979	M	21-84	658	Cancer registry	1,258	Random digit dialing and HCFA	Self-reported occupation
Greenland *et al.* (1994)[a]	US	Mort	Bladder	1969-1984	M	21-90	512	Employee pension records	1,202	Workers at same transformer-manufacturing facility	Job history records and JEM
Siemiatycki *et al.* (1994)	Canada	Inc	Bladder	1979-1986	M	35-70	484	Hospitals	533 population-based and 1,879 cancer controls	Population-based electoral lists and random digit dialing for population controls. Cancer controls were identified from local hospitals	Interview and self-reported job history
Pesch *et al.* (2000)	Germany	Inc	Urothelial carcinoma	1991-1995	B	Cases median (male 69yrs, female 76yrs), Controls median (male 63 yrs female, 67 yrs.)	1,035	Population-based enrollment *via* large hospitals in the study areas	4,298	Local residency registries	Interview, self-reported job history, JEM

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Study	Location	Outcome Type	Cancer Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (yrs)	Cases		Controls		
							N	Source	N	Source	
Reulen *et al.* (2007)	Belgium	Inc	Bladder	2003-2005	B	40-96	202	Limburg Cancer Registry	390	Random sampling general population of Limburg	Self-reported employment history *via* questionnaire and interview
Christensen *et al.* (2013)	Canada	Inc	Bladder	1979-1985	M	35-70	484	Hospitals	418 population-based, 1455 cancer-based	Population-based electoral lists	Expert assessment of self-reported job history
Hadkhale *et al.* (2017)	Iceland, Norway, Sweden, Finland	Inc	Bladder	1961-2005	B[b]	20-65[c]	113,343	NOCCA	566,715	NOCCA	Occupational codes and NOCCA-JEM

Notes:
B = Both Males and Females; HCFA = Health Care Finance Agency; Inc = Incidence; JEM = Job-Exposure Matrix; M = Males; Mort = Mortality; NOCCA = Nordic Occupational Cancer Database; RCC = Renal Cell Carcinoma; US = United States.
– = Not Reported.
(a) Restricted to white males (Greenland *et al.*, 1994).
(b) Approximately 75% male (Hadkhale *et al.*, 2017).
(c) "Exposure was assumed to start at the age of 20 yrs and end at the index date or at 65 yrs, whichever occurred first" (Hadkhale *et al.*, 2017).

Table D.4 TCE and Bladder Cancer Case-Control Study Results

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Schoenberg *et al.* (1984)	Inc	OR	Never employed as dry cleaning, motor vehicle mechanic or printing worker	–	–	Ref	–	Age and duration of cigarette smoking
			Dry cleaning workers	7	10	1.33 (0.50-3.58)	–	
			Motor vehicle mechanics	55	79	1.26 (0.87-1.84)		
			Printing workers	20	38	0.87 (0.49, 1.54)		
Greenland *et al.* (1994)[a]	Mort	OR	Overall	–	–	0.85 (0.32-2.23)	–	Age and yr of death
Siemiatycki *et al.* (1994)	Inc	OR	**Occupations**					Age, ethnicity, socioeconomic status, smoking, coffee consumption, respondent (self *vs.* proxy)
			<10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textile dyers and finishers	2		0.8 (0.2-3.7)		
			Metal machinists	11		1.1 (0.5-2.0)		
			Construction painters	5		1.2 (0.4-3.2)		
			Other painters	5		1.1 (0.4-3.0)		
			≥10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textile dyers and finishers	2		10.8 (1.0-12.0)		
			Metal machinists	16		1.4 (0.8-2.5)		
			Construction painters	8		1.5 (0.7-3.4)		
			Other painters	4		0.9 (0.3-2.7)		
			Industries					
			<10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textiles	17		1.1 (0.7-1.9)		
			Printing and publishing	2		0.3 (0.1-1.2)		
			Metal fabricating and machining	31		1.4 (0.9-2.1)		
			Chemical production	16		1.1 (0.6-2.0)		
			≥10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textiles	7		1.0 (0.4-2.3)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
			Printing and publishing	2		1.9 (0.9-3.9)		
			Metal fabricating and machining	31		1.2 (0.7-1.8)		
			Chemical production	7		1.0 (0.4-2.3)		
Pesch *et al.* (2000)	Inc	OR	**German JEM TCE Exposure Index**[c]					Age, study center, smoking status
			Males					
			Medium	154	–	1.1 (0.8-1.3)	–	
			High	182	–	1.1 (0.9-1.4)		
			Substantial	68	–	1.3 (0.9-1.7)		
			Females					
			Medium	21	–	1.0 (0.6-1.7)	–	
			High	32	–	1.6 (1.0-2.5)		
			Substantial	3	–	0.6 (0.2-2.3)		
			JTEM TCE Exposure Index (Males)					
			Medium	47	–	0.8 (0.6-1.2)	–	
			High	74	–	1.3 (0.9-1.7)		
			Substantial	36	–	**1.8 (1.2-2.7)**		
Reulen *et al.* (2007)	Inc	OR	Textile garment workers	9	22	1.6 (0.6-4.1)	–	Age, sex, smoking, and education
			Building finishers and related trades workers	15	12	1.9 (0.8-4.5)		
			Metal, machinery and related trades workers	37	54	1 (0.6-1.7)		
			Machinery mechanics and fitters	13	25	0.7 (0.3-1.4)		
			Metal trades workers	15	17	1.2 (0.6-2.8)		
			Automobile Mechanics	5	10	0.6 (0.2-1.9)		
			Industrial machinery mechanics	8	16	0.7 (0.3-1.7)		
			Machine operators and assemblers	17	40	0.6 (0.3-1.2)		
			Mechanical machinery assemblers	4	18	0.3 (0.1-1.1)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Christensen *et al.* (2013)	Inc	OR	Never exposed chlorinated solvents	134	Population: 403 Cancer: 1,497	Ref	–	Smoking status; age; income; level of education; ethnicity; questionnaire type (self-reported *vs.* proxy); coffee intake, and aromatic amines exposure
			Any TCE exposure	10	Population: 15 Cancer: 57	0.7 (0.3–1.4)		
			Substantial TCE exposure	5	Population: 9 Cancer: 30	0.6 (0.2–1.5)		
Hadkhale *et al.* (2017)	Inc	HR	**All Participants, Cumulative Exposure (ppm) - 10 Yr Lag[d]**					Age, sex, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			Unexposed	–	–	Ref.	0.07	
			<32.80	3,433	15,884	**1.07 (1.02-1.12)**		
			32.80-129.50	2,714	12,738	1.07 (1.00-1.13)		
			>129.50	759	3,097	**1.23 (1.12-1.40)**		
			Diagnosed at <50 Yrs of Age, Cumulative Exposure (ppm) - 10 Yr Lag[d]					Sex, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			Unexposed	–	–	Ref.	0.44	
			<32.80	873	3,858	**1.11 (1.02-1.22)**		
			32.80-129.50	1,293	5,868	**1.12 (1.03-1.21)**		
			>129.50	569	2,375	**1.24 (1.10-1.40)**		
			Diagnosed at >50 Yrs of Age, Cumulative Exposure (ppm) - 10 Yr Lag[d]					
			Unexposed	–	–	Ref.	0.40	
			<32.80	2,560	12,026	1.04 (1.00-1.10)		
			32.80-129.50	1,421	6,870	1.01 (0.94-1.09)		
			>129.50	190	722	**1.27 (1.02-1.60)**		
			Male, Cumulative Exposure (ppm) - 10 Yr Lag[d]					Age, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents,
			Unexposed	–	–	Ref.	**0.03**	
			<32.80	3,090	14,391	**1.06 (1.01-1.12)**		
			32.80-129.50	2,588	12,179	**1.07 (1.02-1.14)**		
			>129.50	663	2,656	**1.25 (1.13-1.40)**		
			Females, Cumulative Exposure (ppm) - 10 Yr Lag[d]					

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
			Unexposed	–	–	Ref.	0.67	perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			<32.80	343	1,493	1.01 (0.83-1.23)		
			32.80-129.50	126	559	0.96 (0.71-1.30)		
			>129.50	96	441	0.93 (0.50-1.74)		

Notes:
CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; JEM = Job Exposure Matrix; JTEM = Job Task Exposure Matrix; Mort = Mortality; Ref = Reference; OR = Odds Ratio, Pop'n = Population; PPM = Parts Per Million; Yr = Yr.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Restricted to white males (Greenland *et al.*, 1994)
(b) "For each occupation or industry, the reference (unexposed) group consisted of all those who did not work in that occupation or industry Siemiatycki *et al.* (1994).
(c) Exposure categories defined by 30th, 60th, and 90th percentiles of the distribution of duration of exposure (in years) among exposed controls (Pesch *et al.*, 2000).
(d) Authors noted running models with no lag and a 20-yr lag, but did not report the results (Hadkhale *et al.*, 2017).

Table D.5 TCE and Bladder Cancer Meta-analyses and Pooled Study Results

Citation	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
Wartenberg *et al.* (2000)	Meta-analysis	Inc	Bladder	3	Cohort	IVW	Tier I[a]	SIR	1.0 (0.6-1.6)
		Mort		4				SMR	1.1 (0.7-1.5)
		Inc		2			Tier II[b]	SIR	1.0 (0.5-2.1)
		Mort		5				SMR	1.1 (0.8-1.5)
		Inc		1			Tier III[c]	SIR	0.8 (0.5-1.3)
		Mort		4			Tier IV[d]	SMR	**2.0 (1.3-2.9)**
Kogevinas *et al.* (2003)	Pooled	Inc	Bladder	11	Case-control	Unconditional logistic regression	Automobile mechanic	OR	**1.38 (1.02-1.87)**
							Printers and related workers		**1.45 (1.07-1.97)**
							Launderers, dry-cleaners and pressers		1.24 (0.67-2.31)
							Metal processers		1.14 (0.93-1.39)
							Textile workers		1.05 (0.81-1.36)
Hansen *et al.* (2013)	Pooled	Inc	Bladder	3	Cohort	Poisson	Men & women	SIR	1.17 (0.75-1.26)
Sciannameo *et al.* (2018)	Pooled	Inc	Bladder	2	Case-control	Logistic regression	Never exposed	OR	Ref
							Ever exposed		1.21 (0.98-1.50)
							Cumulative Exposure Level[e]		
							None	OR	Ref
							Low		1.30 (1.00-1.72)
							High		1.15 (0.87-1.52)

Notes:
CI = Confidence Interval; Inc = Incidence; ISCO= International Standard Classification of Occupations; IVW = Inverse Variance-Weighted; JEM = Job-Exposure Matrix; Mort = mortality; NEC = Not Otherwise Classified; OR = Odds Ratio; Ref = Reference; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene.
– = Not Reported.
((a) "Tier I studies are those which TCE exposure has been inferred for individual study subjects and best characterized - such as biomarkers and JEMs and studies that conducted other worksite exposure evaluations such as walkthroughs." Wartenberg *et al.* (2000)
(b) "Tier II studies are those in which there is putative TCE exposure, but individuals are not identified as uniquely exposed to TCE." Wartenberg *et al.* (2000)
(c) "Tier III studies are studies of dry cleaner and laundry workers in which subjects are exposed to a variety of solvents including TCE." Wartenberg *et al.* (2000)
(d) Wartenberg *et al.* (2000) lists this result in Table 9 under "Tier IV cohort" studies, but Tier IV is not described in the text and the included studies are listed as Tier III studies in Table 3.
(e) Cumulative exposure levels defined as "low" for values < median in controls and "high" otherwise (Sciannameo *et al.*, 2018).

Attachment E

TCE Toxicity Studies

List of Tables

Table E.1 TCE and Bladder Cancer Chronic Oral Study Results

Table E.2 TCE and Bladder Cancer Chronic Inhalation Study Results

Table E.3 TCE and Bladder Cancer Chronic Toxicity Study Quality Overview

Table E.4 TCE and Bladder Cancer Chronic Toxicology Study Quality Assessment

Table E.1 TCE and Bladder Cancer Chronic Oral Study Results

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
NCI (1976)[a]	Osborne-Mendel rats	78	110	20 M	0	0/20	0/20
				50 M	549	0/46	0/46
					1,097	0/46	0/46
				20 F	0	0/18	0/18
				50 F	549	0/42	0/42
					1,097	0/43	0/43
	B6C3F1 mice		90	20 M	0	0/20	0/20
				50 M	1,169	0/48	0/48
					2,339	0/47	0/47
				20 F	0	0/19	0/19
				50 F	869	0/48	0/48
					1,739	0/44	0/44
Henschler *et al.* (1984)[b]	Swiss (ICR/HA) mice	72	106 weeks	50 M	0	NR	NR
					2,400 (TCE industrial)	NR	NR
					2,400 (TCE pure)	NR	NR
					2,400 (TCE + EB)	NR	NR
					2,400 (TCE + EPC)	NR	NR
					2,400 (TCE + EB + EPC)	NR	NR
				50 F	0	NR	NR
					1,800 (TCE industrial)	NR	NR
					1,800 (TCE pure)	NR	NR
					1,800 (TCE + EB)	NR	NR
					1,800 (TCE + EPC)	NR	NR
					1,800 (TCE + EB + EPC)	NR	NR
Maltoni *et al.* (1986, 1988a)	Sprague-Dawley rats	52	Until natural death	30 M	0	NR	NR
					50	NR	NR

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
					250	NR	NR
				30 F	0	NR	NR
					50	NR	NR
					250	NR	NR
NTP (1988)[c]	ACI rats	103	103	50 M	0	0/44	1/44
					500	1/47	1/47
					1,000	1/42	0/42
				50 F	0	0/50	0/50
					500	0/50	0/50
					1,000	0/46	0/46
	August rats			50 M	0	1/50	1/50
					500	0/47	0/47
					1,000	0/44	0/44
				50 F	0	0/50	0/50
					500	0/50	0/50
					1,000	0/50	0/50
	Marshall rats			50 M	0	0/45	0/45
					500	0/41	0/41
					1,000	0/44	0/44
				50 F	0	0/46	0/46
					500	1/40	0/40
					1,000	0/40	0/40
	Osborne-Mendel rats			50 M	0	0/50	0/50
					500	0/50	0/50
					1,000	0/50	0/50
				50 F	0	0/48	0/48
					500	0/49	0/49
					1,000	0/50	0/50

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
NTP (1990)[d]	F344/N rats	103	103	50 M	0	0/50	0/50
					500	0/50	0/50
					1,000	0/49	0/49
				50 F	0	0/50	0/50
					500	0/50	0/50
					1,000	0/50	0/50
	B6C3F1 mice			50 M	0	0/50	0/50
					1,000	0/50	0/50
				50 F	0	0/48	0/48
					1,000	0/49	0/49

Notes:
F = Female; M = Male.
NR = bladder was analyzed, but bladder tumor findings were not reported.
(a) I used the number of bladder tissues examined, as reported in Tables XXVIIIa (rats) and XXVIIIb (mice), as denominators. NCI (1976) utilized a technical-grade TCE that contained two stabilizer compounds that are known carcinogens (epichlorohydrin and 1,2-epoxybutane).
(b) The exposure duration of 72 weeks is based on US EPA (2011). Henschler *et al.* (1984) exposed mice to a single dose of TCE with or without the stabilizer compounds, triethanolamine, 1,2-epoxybutane, or both. The stabilizer compound 1,2-epoxybutane is a known carcinogen. Due to overt toxicity attributable to gavage protocol, the exposures were non-continuous (stopped for all groups during weeks 35-40, 65, and 69-78) and doses were reduced by a factor of 2 from week 40 onward.
(c) I used the number of animals necropsied when the denominators for incidences were not specified. NTP (1988) stated that "the doses of trichloroethylene selected for the 2-year studies were too high," that animals in each treatment group had reduced survival, including "a large number of accidental deaths" in the high dose group due to accidental gavage error, and that there was incomplete documentation of the experimental data. NTP (1988) concluded that "the studies are considered inadequate for either comparing or assessing trichloroethylene-induced carcinogenesis in these strains of rats."
(d) I used the number of animals necropsied when the denominators for incidences were not specified. NTP (1990) concluded that the results in male F344/N rats were "equivocal for detecting a carcinogenic response because both groups receiving TCE showed significantly reduced survival compared to vehicle controls (35/150, 70%; 20/150, 40%; 16/50, 32%) and because 20% of the animals in the high dose group were killed accidently by gavage error."

Table E.2 TCE and Bladder Cancer Chronic Inhalation Study Results

Citation	Strain/ Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Concentration (ppm)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
Henschler *et al.* (1980)	Han:WIST rats	78	156	30 M	0	0/29	0/29
					100	0/30	0/30
					500	0/30	1/30
				30 F	0	0/28	0/28
					100	1/30	0/30
					500	0/30	0/30
	Han:NMRI mice		130	30 M	0	0/30	0/30
					100	0/29	0/29
					500	0/30	0/30
				30 F	0	0/29	0/29
					100	0/30	0/30
					500	0/28	0/28
	Syrian hamsters			30 M	0	0/30	0/30
					100	0/30	0/30
					500	0/30	0/30
				30 F	0	0/30	0/30
					100	0/29	0/29
					500	0/30	0/30

Citation	Strain/ Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Concentration (ppm)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni *et al.* (1986, 1988a)	Sprague-Dawley rats	104	Until natural death	40M	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
				40F	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
	Sprague-Dawley rats			90-95 M	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
				90-105 F	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
	B6C3F1 mice	78		90 M	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
				90 F	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
	Swiss mice			90 M	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR
				90 F	0	NR	NR
					100	NR	NR
					300	NR	NR
					600	NR	NR

Notes:
F = Female; M = Male; ppm = Parts per Million.

NR = Bladder was analyzed, but bladder tumor findings were not reported.

Table E.3 TCE and Bladder Cancer Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most studies reported sufficient information on the species, test article name, experimental design, exposure conditions, and outcome evaluation methods. NTP (1988) stated, "There was insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data. Also, individual animal identification was not always verifiable." Some studies that examined the bladder did not report any bladder tumor data (Maltoni *et al.*, 1986, 1988a)).
Allocation	Animals were randomly allocated to dose groups in the majority of chronic studies, with the exception of Henschler *et al.* (1980).
Bias	Two chronic oral gavage studies conducted by NTP (1988, 1990) were concluded by the agency to be insufficient to evaluate the potential carcinogenicity of TCE due, in part, to reduced survival in high dose group from accidental gavage error, and the testing of high doses. NCI (1976) exposed mice to TCE that contained two stabilizer compounds (epichlorohydrin and 1,2-epoxybutane) known to be carcinogenic, and high early mortality was observed due to the testing of high doses. In addition, Henschler *et al.* (1984) exposed mice to TCE that contained 1,2-epoxybutane as a stabilizer. No other studies indicated differences across treatment groups that could bias results.
Sample	Studies had adequate sample sizes, with the exception of NCI (1976) (controls), Henschler *et al.* (1980), and Maltoni *et al.* (1986, 1988a)(for oral exposure and experiment BT304 bis).
Chemical Administration and Characterization	All studies provided adequate information on chemical source, purity, and composition, and independently verified chemical purity or took steps to ensure reported exposure levels were accurate, with the exception of NCI (1976), in which exposure levels were not verified.
Exposure Conditions	The exposure duration was too short for assessing carcinogenicity in rats in four chronic oral studies (NCI, 1976; Maltoni *et al.*, 1986, 1988a; NTP, 1988; NTP, 1990) and one chronic inhalation study (Henschler *et al.*, 1980) rats were exposed for 78 weeks in NCI (1976) and Henschler *et al.* (1980), 52 weeks (oral exposure) in Maltoni *et al.* (1986, 1988a), and 103 weeks in NTP (1988) and NTP (1990). The exposure period was too short for assessing carcinogenicity (72 weeks) in mice in one chronic oral study (Henschler *et al.*, 1984). In one additional chronic oral study (NTP, 1990), the exposure duration was too long: mice were exposed 103 weeks. Therefore, the studies have limited human relevance. In an additional chronic study (Henschler *et al.*, 1984), only one dose was tested per sex, and the exposures were non-continuous due to overt toxicity attributable to gavage protocol (stopped for all groups during weeks 35-40, 65, and 69-78), and doses were reduced by a factor of 2 from week 40 onward.
Outcome Assessment	In some chronic studies, there was a reliable, valid, sensitive, and specific outcome assessment method and an appropriate observation period. However, five studies (Henschler *et al.*, 1980; Maltoni *et al.*, 1986, 1988a; NCI, 1976; NTP, 1990; Henschler *et al.*, 1984) had observation periods which were too long. Henschler *et al.* (1980) observed rats until 156 weeks (78 weeks post-exposure), and hamsters and mice until 130 weeks (52 weeks post-exposure). Maltoni *et al.* (1986, 1988a) examined animals after "spontaneous death." NTP (1990) observed mice and rats until 103 weeks, which is too long for mice and too short for rats. NCI (1976) observed rats and mice until 110 weeks (32 weeks post-exposure) and 90 weeks (12 weeks post-exposure). Finally, Henschler *et al.* observed mice for 106 weeks (34 weeks post-exposure). In these bioassays, animals were observed either over their entire lifetimes, when moribund, or following spontaneous death, which could have biased results. In addition, Maltoni *et al.* (1986, 1988a) used statistical methods that did not account for the extended observation period (Gift *et al.*, 2013).

Table E.4 TCE and Bladder Cancer Chronic Toxicology Study Quality Assessment

Citation	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
NCI (1976)	**Reporting** **Allocation** **Exposure Conditions** (mice)	**Bias:** TCE contained two stabilizer compounds that are carcinogens; high early mortality in rats due to testing high doses **Sample:** Small sample size (controls) **Chemical Administration and Characterization:** Did not verify exposure levels **Exposure Conditions:** Exposure duration too short (rats) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Henschler *et al.* (1984)	**Allocation** **Sample** **Chemical Administration and Characterization**	**Reporting:** No bladder tumor data **Bias:** TCE contained a stabilizer compound that is carcinogenic **Exposure Conditions:** Non-continuous exposure; only one dose tested per sex; exposure duration too short **Outcome Assessment:** Exposures were intermittent and doses were reduced due to overt toxicity from initial dosing protocols; observation period too long	**None:** No bladder tumor data
Maltoni *et al.* (1986, 1988a)	**Allocation** **Bias** **Chemical Administration and Characterization**	**Reporting:** No bladder tumor data **Sample:** Small sample size **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long; improper statistics	**None:** No bladder tumor data
NTP (1988)	**Allocation** **Sample** **Chemical Administration and Characterization**	**Reporting:** Insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data **Bias:** Reduced survival in high dose groups due to gavage error; tested doses were too high, resulting in mortality **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too short	**Limited:** Low study quality
NTP (1990)	**Reporting** **Allocation** **Sample** **Chemical Administration and Characterization**	**Bias:** Reduced survival in high dose group due to gavage error; tested doses were too high, resulting in mortality **Exposure Conditions:** Exposure duration too long (mice); too short (rats) **Outcome Assessment:** Observation period too long (mice) ; too short (rats)	**Limited:** Low study quality
Chronic – Inhalation			

Citation	Strengths	Weaknesses	Human Relevance
Henschler *et al.* (1980)	**Reporting Bias** **Chemical Administration and Characterization** **Exposure Conditions** (mice and hamsters)	**Allocation:** Did not specify whether random **Sample**: Small sample size **Exposure Conditions:** Exposure duration too short (rats) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Maltoni *et al.* (1986, 1988a)	**Allocation** **Bias** **Sample** **Chemical Administration and Characterization** **Exposure Conditions**	**Reporting:** No bladder tumor data **Outcome Assessment:** Observation period too long; improper statistics	**None:** No bladder tumor data

Notes:
NCI = National Cancer Institute; NTP = National Toxicology Program; TCE = Trichloroethylene.

Attachment F

PCE Epidemiology Studies

List of Tables

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Table F.5 PCE and Bladder Cancer Meta-analyses and Pooled Study Results

Table F.1 PCE and Bladder Cancer Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Bladder	Death certificate	1942-1980
Travier *et al.* (2002)	Sweden	Dry-cleaning workers	B	–	3,742	1960/1970 census	Census JEM	Inc	Bladder	CERIII	1971-1989
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	$\bar{x}$ = 39.25	86,868	1973-1997	Employment in the factory	Mort	Bladder	National mortality database	1985-1997
Sung *et al.* (2007)	Taiwan	Electronics factory workers	F	–	63,982	1974-1992	Employment at factory	Inc	Bladder	Taiwan National Cancer Registry	1979-2001
Wilson *et al.* (2008)	Sweden	Employed Swedish Residents	B	–	4,197,684	1960/1970 census	JEM	Inc	Bladder	CERIII	1971-1989
Pukkala *et al.* (2009) [Lynge & Thygesen, 1990; Andersen *et al.*, 1999; Ji *et al.*, 2005]	Denmark Finland Iceland Norway Sweden	General population	B	30-64[a]	~14.9 million	1960-1990	Occupation based on first census at age 30-64: Denmark: 1970 Sweden: 1960, 1970, 1980, 1990 Norway: 1960, 1970, 1980 Finland: 1970, 1980, 1990 Iceland: 1981	Inc	Bladder, ureter, & urethra combined	National registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004
Calvert *et al.* (2011) [Brown and Kaplan, 1987; Ruder *et al.*, 1994; 2001]	US	NIOSH cohort of dry cleaners	Both	$\bar{x}$ =34.5[b]	1,704	–	Dry cleaning union records	Mort	Bladder and other urinary organs	Death certificates and NDI	1940-2004

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	Total: 45,318 TCE exposed: 5,443	–	JEM	Mort	Bladder and other urinary	California Death Statistical Master File, NDI, SSA, death certificates, and company records	1960-2008
Seldén and Ahlborg Jr. (2011)	Sweden	Laundry and dry-cleaning workers	B	–	9,440	1973-1983	Questionnaire mailed to all "washing establishments" recorded in Swedish Postal Address Registry	Inc	Bladder	National cancer registry	1985-2006
Bove *et al.* (2014b)	US	Marines & Navy personnel at CL and CP	B	CL and CP: 20-49[c]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Bladder	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics facility workers	B	$\bar{x}$= 25.7-28.7[d]	34,494	1969-2001	Employment at the facility	Mort	Bladder and other urinary organs	SSA, NDI, IRS, and death certificates	1969-2009
ATSDR (2018a)[e]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[f] Civilian Employees CL: 60-64[f] CP: ≥65[c]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines & Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Bladder	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012
Callahan *et al.* (2019) [Blair *et al.*, 1990, 2003]	US	Dry cleaning workers	B	$\bar{x}$ = 36.7[g]	5,369	–	Exposure scores calculated based on job titles from union records	Mort	Bladder	Death certificates, NDI and SSA Death Master File	1948-2014

Notes:

ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; IRS = Internal Revenue Service; Mort = Mortality; NDI = National Death Index; SSA = Social Security Administration; US = United States.

$\bar{x}$ = Mean; – = Not Reported.

When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.

(a) Age at initial census (Pukkala *et al*., 2009).

(b) Age at first employment Calvert *et al*. (2011).

(c) Median age from start to end of follow-up (Bove *et al*., 2014b)

(d) Mean age at hire Silver *et al*. (2014).

(e) Ages and population sizes are reflective of Marines, Navy, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018a).

(f) Median age at survey or death (ATSDR, 2018a).

(g) Age at entry Callahan *et al*. (2019).

Table F.2 PCE and Bladder Cancer Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Blair *et al.* (1989)	US national population	Mort	SMR	Marine inspectors	2	4	0.5 (0.06-1.79)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	0.9 (0.18-2.62)		
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**People Classified with Relevant Occupational or Industrial Code on ≥1 Census**					Sex, age, calendar period, geographic region, and urban setting
				Overall	145	–	1.01 (0.86-1.19)	–	
				People Classified with Relevant Occupational or Industrial Code on Both Censuses					
				Overall	16	–	1.00 (0.61-1.63)	–	
				Females	4		0.59 (0.22-1.57)	–	
				Males	12		1.32 (0.75-2.32)	–	
Chang *et al.* (2003)	Taiwan general population	Mort	SMR	Males	1	1.04	0.96 (0.01-5.36)	–	Age, calendar yr, and sex
				Females	1	1.04	0.96 (0.01-5.33)		
Sung *et al.* (2007)	Taiwanese general population	Inc	SIR	Female workers	3	8.8	0.34 (0.07-1.00)	–	Age and calendar yr
Wilson *et al.* (2008)	Swedish employed population	Inc	SIR	**Laundry Workers (Occupation)**					Age, sex, and calendar yr
				Females	37	–	1.07 (0.75-1.47)	–	
				Males	31		1.23 (0.83-1.74)		
				Laundering, Ironing, and Dyeing (Industry)					
				Females	55	–	1.18 (0.89-1.53)	–	
				Males	55		1.15 (0.87-1.50)		
Pukkala *et al.* (2009)	Employed population in Denmark, Finland, Iceland, Norway, and Sweden	Inc	SIR	**Launderers**					Country, sex, age, and 5-yr calendar periods
				Males	186	–	1.10 (0.95-1.27)	–	
				Females	248		1.07 (0.95-1.22)		
Calvert *et al.* (2011)	US national population	Mort	SMR	Overall	10	–	1.81 (0.87-3.33)	–	Age, sex, race, and calendar time
				PCE-only (worked only in shops where PCE was primary cleaning solvent)	0		–		
				PCE-plus (worked in PCE-only shops and shops mainly using other solvents)	10		**2.59 (1.24-4.76)**		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				Time since first employment and duration of employment (yrs) in PCE-using shops					
				Time < 20 Duration 1-5	0	–	–	–	
				Time < 20 Duration ≥ 5	0				
				Time ≥ 20 Duration 1-5	1		0.53 (0.03-2.52)	0.12	
				Time ≥ 20 Duration ≥ 5	9		**4.08 (2.13-7.12)**		
Lipworth *et al.* (2011)	California general population (white workers), US general population (non-white workers)	Mort	SMR	Factory workers exposed to PCE	17	20.2	0.84 (0.49–1.35)	–	Race, age, calendar yr, and sex
Seldén and Ahlborg Jr. (2011)	Swedish national population	Inc	SIR	Overall	38	–	0.92 (0.65-1.26)	–	Age, sex, and calendar yr
				Females	20		0.98 (0.60-1.52)		
				Males	18		0.86 (0.51-1.36)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-155)[b]	4	–	0.75 (0.24-2.33)	–	
				Medium/high (>155-8,585)[b]	7		0.89 (0.35-2.22)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[c]			Low (>1-155)	1		0.55 (0.06-5.35)		
				Medium (>155-380)	3		1.62 (0.32-8.10)		
				High (>380-8,585)	3		1.24 (0.25-6.21)		
Silver *et al.* (2014)	Workers of full risk set	Mort	HR	Cumulative PCE exposure	–	–	0.89 (0.37-2.13)	–	Pay code, age, and sex
	US population and New York State (without NYC) population		SMR	**Hourly Employees**					Age, sex, calendar period, and pay code
				Males	32	–	1.02 (0.70-1.44)	–	
				Females	13		0.63 (0.34-1.09)		
				Salaried Employees					
				Males	3	–	0.81 (0.17-2.36)	–	
				Females	0		0.00 (0.00-14.3)		
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low (0-<36)	93	–	1.33 (0.80-2.24)	–	
				Medium (36-<711)	59		1.30 (0.76-2.23)		
				High (≥711)	30		**2.07 (1.12-3.82)**		
	CL Marines & Navy personnel with low exposure (>0-<36 µg/L-mos)			Medium (36-<711)	59		0.99 (0.69-1.40)		
				High (≥711)	30		1.54 (0.99-2.41)		
	CP civilian employees			**CL Civilian Employees**					None
				Cumulative exposure level (µg/L-mos)[d,e]					
				Low (<457)	8	–	1.02 (0.41-2.54)	–	
				Medium (457-<2,118)	2		0.32 (0.07-1.45)		
				High (≥2,118)	3		1.81 (0.50-6.53)		
	CL civilian employees with low exposure (<457 µg/L-mos)			Medium (457-<2,118)	2		0.32 (0.07-1.50)		
				High (≥2,118)	3		1.78 (0.47-6.77)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Callahan *et al*. (2019)	US general population	Mort	SMR	Dry cleaning workers	15	14	1.1 (0.6-1.8)	–	Age, sex, race, yr of enrollment in the union, and calendar period
				Yr Joined Union					
				< 1960	11	11	1.0 (0.5-1.8)	–	
				> 1960	4	3	1.5 (0.4-3.7)		
	No/low exposure group		HR	**PCE Exposure**					Age, race, sex, and decade of enrollment
				10-Yr Lag					
				Medium	6	–	2.3 (0.6-8.3)	0.09	
				High	3		5.2 (0.9-30.4)		
				20-Yr Lag					
				Medium	5	–	4.2 (0.7-24.5)	0.08	
				High	3		**9.2 (1.1-76.7)**		
	Tertile 1			**Cumulative Estimated Solvent Exposure**					
				10-Yr Lag					
				Tertile 2	3	–	0.7 (0.2-3.2)	0.17	
				Tertile 3	7		1.9 (0.5-7.6)		
				20-Yr Lag					
				Tertile 2	1	–	0.4 (0.0-5.0)	0.05	
				Tertile 3	7		3.2 (0.6-18.4)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; NYC = New York City; OR = Odds Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; µg/L = Micrograms per Liter; US = United States; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Exposure groups are unclear in Bove *et al*. (2014b). Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)." I report the values consistent with the text definition.
(c) To evaluate exposure-response relationships, Bove *et al*. (2014b) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(d) ATSDR (2018a) categorized as low exposure (< 50th percentile), medium exposure (⩾50th percentile to <90th percentile), and high exposure (⩾90th percentile) ; for female Marines and Navy personnel, cut points were based on the 75th (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos.
(e) The correlation between TCE and PCE was approximately 1 in ATSDR (2018a).

Table F.3 PCE and Bladder Cancer Case-Control Study Characteristics

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (yrs)	Cases		Controls		
							N	Source	N	Source	
Schoenberg *et al.* (1984)	US	Inc	Urinary bladder or papilloma not specified as benign	1978-1979	M	21-84	658	Cancer registry and hospital pathology records	1,258	RDD and HCFA	Self-reported occupation
Smith *et al.* (1985)	US	Inc	Bladder	1977-1978	B	21-84	–	National Bladder Cancer Study	–	–[a]	Interview, questionnaire
Silverman *et al.* (1989a)	US	Inc	Bladder	1977-1978	M	21-84	2,100	National Bladder Cancer Study	3,874	RDD (21-64 yrs of age) and stratified random sampling from the HCFA population lists (65-84 yrs of age	Interview, questionnaire, job coding using the US Bureau of the Census index of industries and occupations
Silverman *et al.* (1989b)	US	Inc	Bladder	1977-1978	M	21-84	126	National Bladder Cancer Study	383	RDD (21-64 yrs of age) and stratified random sampling from the HCFA lists (65-84 yrs of age)	Interview, questionnaire, job coding using the US Bureau of the Census index of industries and occupations
Silverman *et al.* (1990)	US	Inc	Bladder	1977-1978	F	21-84	652	National Bladder Cancer Study	1,266	RDD (21-64 yrs of age) and stratified random sampling from the HCFA lists (65-84 yrs of age)	Interview, questionnaire, job coding using the US Bureau of the Census index of industries and occupations
Steineck *et al.* (1990)	Sweden	Inc	Urothelial	1985-1987	M	–	256	–	287	Computerized register	Self-reported employment and industry
Burns and Swanson (1991)	US	Inc	Bladder	–	B	40-84	2,160	Metropolitan Detroit Cancer Surveillance System	3,979	Metropolitan Detroit Cancer Surveillance System	Interview, job coding using the 1980 US Census Bureau classification
Aschengrau *et al.* (1993)	US	Inc	Bladder	1983-1986	B	–	61	Massachusetts Cancer Registry	852	RDD, HCFA, and death certificates	Modeled dose based on residential history, distributions system, and pipe characteristics
Siemiatycki *et al.* (1994)	Canada	Inc	Bladder	1979-1986	M	35-70	484	Hospitals	533 population-based and 1,879 cancer controls	Population-based electoral lists and RDD for population controls. Cancer controls were identified from local hospitals	Interview, self-reported job history

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Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (yrs)	Cases		Controls		
							N	Source	N	Source	
Swanson and Burns (1995)	US	Inc	Bladder	1984-1991	F	40-84	627	Cancer surveillance system	1,972	Randomly generated phone number list	Self-reported by subject or proxy and occupation coded according to 1980 US census
Teschke *et al.* (1997)	Canada	Inc	Bladder	1990-1991	B	≥19	105	British Columbia Cancer Agency	139	British Columbia provincial voters list	Interview, questionnaire
Pesch *et al.* (2000)	Germany	Inc	Urothelial carcinoma	1991-1995	B	Cases M: 69 F: 76 Controls M: 63 F: 67 (median)	1,035	Population-based enrollment *via* large hospitals in the study areas	4,298	Local residency registries	Interview, self-reported job history, JEM
Zheng *et al.* (2002)	US	Inc	Bladder	1986-1989	B	40-85	1,452	State health registry	2,434	State driver's license records and HCFA	Self-reported job history
Colt *et al.* (2004)	US	Inc	Bladder	1994-1998	M	25-74	331	NH State Cancer Registry	407	July 1993-June 1995: shared a control group with a non-melanoma skin cancer study; July 1995-June 1997: controls selected from the NH DoT (<65 yrs) or CMS of NH (>65 yrs)	Self-reported job history coded using the Standard Occupational Classification Manual scheme from in-person interview and questionnaire
Gaertner *et al.* (2004)	Canada	Inc	Bladder	1994-1997	M	20-74	535	Provincial cancer registries	1,430	RDD, provincial health insurance plan databases	Self-reported employment history *via* questionnaire and interview
Lynge *et al.* (2006)	Denmark, Norway, Sweden, Finland	Inc	Bladder	1970-2001	B	–	Total: 353 M: 177 F: 176	National population, death, and cancer registries	1,482	Laundry and dry-cleaning workers cohort	1970 census, interviews, pension schemes, and industry and telephone books

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (yrs)	Cases		Controls		
							N	Source	N	Source	
Reulen *et al.* (2007)	Belgium	Inc	Bladder	2003-2005	B	40-96	202	Limburg Cancer Registry	390	Random sampling general population of Limburg	Self-reported employment history *via* questionnaire and interview
Dryson *et al.* (2008)	New Zealand	Inc	Bladder	2003-2004	B	25-70	213	New Zealand Cancer Registry	471	New Zealand Electoral Roll	Employment history from interview/ questionnaire
Colt *et al.* (2011)	Maine New Hampshire Vermont	Inc	Urothelial carcinoma of the bladder	2001-2004	B	30-79	1,158	Hospital pathology departments, hospital and state cancer registries	1,402	State DMV records (ages 30-64) and the CMMS (ages 65-79)	Self-reported employment history *via* questionnaire and interview
Christensen *et al.* (2013)	Canada	Inc	Bladder	1979-1985	M	35-70	484	Hospitals	Population: 418 Cancer: 1455	Population-based electoral lists	Expert assessment of self-reported job history
Hadkhale *et al.* (2017)	Iceland, Norway, Sweden, Finland,	Inc	Bladder	1961-2005	B[b]	20-65[c]	113,343	NOCCA	566,715	NOCCA	Occupational codes and NOCCA-JEM

Notes:
B = Both Males and Females; CMS = Centers for Medicare and Medicaid Services; DOT = Department of Transportation; DMV, Department of Motor Vehicle; F = Females; Inc = Incidence; JEM = Job Exposure Matrix; M = Males; Mort = Mortality; NH = New Hampshire; NOCCA = Nordic Occupational Cancer Database; RDD = Random Digit-dialing.
– = Not Reported.
(a) Unclear what the source population of the controls was. The only information provided was that the controls had participated in the National Bladder Cancer Study (Smith *et al.*, 1985).
(b) Approximately 75% male (Hadkhale *et al.*, 2017).
(c) Hadkhale *et al.* (2017) stated, "Exposure was assumed to start at the age of 20 yrs and end at the index date or at 65 yrs, whichever occurred first."

Table F.4 PCE and Bladder Cancer Case-Control Study Results

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
Schoenberg *et al.* (1984)	Inc	OR	Never employed in respective occupation	–	–	Ref	–	Age and duration of cigarette smoking
			Ever employed as dry cleaning worker	7	10	1.33 (0.50-3.58)		
			Ever employed as fabricated textile worker	28	31	1.67 (0.97-2.87)		
Smith *et al.* (1985)	Inc	RR	**Laundry and Dry Cleaning Workers**[a]					
			Not laundry or drycleaning working & non-smoker	–	–	Ref	–	Age, sex, and smoking status
			Nonsmoker			1.31 (0.85-2.03)		
			Former smoker			**2.99 (1.80-4.97)**		
			Current smoker			**3.94 (2.39-6.51)**		
Silverman *et al.* (1989a)	Inc	RR	Never employed in respective occupation	–	–	Ref	–	Smoking
			All mechanics	353	533	1.2 (1.0-1.4)		
			Auto mechanic in trucking service industry	11	2	**10.2 (2.1-68.6)**		
			All metal working and fabrication workers	477	755	1.1 (1.0-1.3)		
			Textile worker	38	111	**0.6 (0.4-0.9)**		
			Dyer	7	21	0.6 (0.2-1.4)		
Silverman *et al.* (1989b)	Inc	RR	Never employed in respective occupation	–	–	Ref	–	Smoking, other high-risk occupations
			Dry cleaner, ironer, presser	11	12	**2.8 (1.1-7.4)**		
			Summary mechanic	13	32	1.1 (0.5-2.5)		
			Auto mechanic	6	15	1.4 (0.4-4.4)		
			Summary metal working and fabrication occupation	13	39	1.0 (0.5-2.0)		Smoking
			Auto worker	10	18	2.3 (0.8-6.4)		
			Dry cleaner, Ironer, Presser					
			Never	–	–	Ref	0.16	Age and smoking
			< 5 Yrs	7	5	5.3 (-)		
			≥ 5 Yrs	4	7	1.8 (-)		
Silverman *et al.* (1990)	Inc	RR	Never employed in respective occupation	–	–	Ref	–	Smoking
			Dry cleaner, ironer, presser	23	32	1.4 (0.8-2.5)		
			Summary printer	1	10	0.2 (<0.1-1.4)		
			Summary metal machinery worker	87	122	1.4 (1.0-1.9)		
			Summary metal working and fabrication	31	35	1.5 (0.9-2.6)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
			Metal fabrication, assembly, repair worker	11	7	2.5 (0.9-7.4)		
			Textile worker	14	50	0.6 (0.3-1.1)		
			Chemical processing worker	13	12	2.1 (0.9-5.1)		
			Auto worker	7	6	2.1 (0.6-7.5)		
			Duration of Employment (Yrs)					Smoking and age
			Metal fabrication, assembly, repair workers					
			Never	–	–	Ref	**0.021**	
			< 5	9	4	3.5 (–)		
			≥ 5	2	2	2.1 (–)		
			Textile workers					
			Never	–	–	Ref	**0.031**	
			<5	6	19	0.6 (–)		
			5-9	5	15	0.7 (–)		
			≥ 10	3	14	0.4 (–)		
Steineck *et al.* (1990)	Inc	RR	**Urothelial Cancer**					Yr of birth and smoking
			Not employed as dry cleaner	–	–	Ref	–	
			Dry cleaner	2	2	1.2 (0.2-9.2)		
Burns and Swanson (1991)	Inc	OR	**Occupation**					Cigarette smoking, race, gender, and age at diagnosis
			Unexposed[c]	812	2,048	Ref	–	
			Mechanics	50	50	1.2 (0.8-1.9)		
			Dry cleaning workers	8	14	1.9 (0.7-4.9)		
			Industry					
			Unexposed[c]	779	1,198	Ref	–	
			Textile manufacturing	6	12	0.9 (0.3-2.6)		
			Printing	22	41	0.7 (0.4-1.2)		
			Chemical manufacturing	13	20	0.6 (0.3-1.2)		
			Automobile manufacturing	506	709	0.9 (0.7-1.0)		
			Dry cleaners and laundries	15	27	1.2 (0.6-2.4)		
Aschengrau *et al.* (1993)	Inc	OR	Never	–	–	Ref	–	Sex; age at diagnosis (cases) or index yr (controls); vital status at interview; educational level; occupational PCE, benzene, & other solvent exposures; smoking status; previous urinary tract infection or kidney stones
			Any	13	127	1.39 (0.67-2.91)		
			Any, mostly bathing	–	–	1.99 (0.40-10.01		
			High (>90th percentile)	4	10	4.03 (0.65-25.10)		
	Inc	OR	**Occupation**					

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
Siemiatycki *et al.* (1994)			*<10 yrs exposure*					Age, ethnicity, socioeconomic status, smoking, coffee consumption, respondent (self *vs.* proxy)
			Unexposed[b]	–	–	Ref	–	
			Textile dyers and finishers	2		0.8 (0.2-3.7)		
			Metal machinists	11		1.1 (0.5-2.0)		
			≥10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textile dyers and finishers	2		10.8 (1.0-12.0)		
			Metal machinists	16		1.4 (0.8-2.5)		
			Industry					
			<10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textiles	17		1.1 (0.7-1.9)		
			Printing and publishing	2		0.3 (0.1-1.2)		
			Metal fabricating and machining	31		1.4 (0.9-2.1)		
			Chemical production	16		1.1 (0.6-2.0)		
			≥10 yrs exposure					
			Unexposed[b]	–	–	Ref	–	
			Textiles	7		1.0 (0.4-2.3)		
			Printing and publishing	2		1.9 (0.9-3.9)		
			Metal fabricating and machining	31		1.2 (0.7-1.8)		
			Chemical production	7		1.0 (0.4-2.3)		
Swanson and Burns (1995)	Inc	OR	Unexposed[c]	–	–	Ref	–	Smoking, sex, race, and age at interview
			Dry cleaning	6	16	2.0 (0.7-6.2)		
Teschke *et al.* (1997)	Inc	OR	Never employed in respective occupation (<6 mos)	–	–	Ref	–	Sex, age, smoking status
			Laundry personnel, ever employed (≥ 6 mos)	5	4	2.3 (0.4-13.9)		
			Laundry personnel, most recent 20 yrs employment removed	4	4	1.8 (0.3-11.3)		
Pesch *et al.* (2000)	Inc	OR	**German JEM by PCE Exposure Index**					Age, study center, smoking status
			Males					
			Unexposed and low[d]	–	–	Ref	–	
			Medium	162		1.1 (0.9-1.3)		
			High	172		1.2 (1.0-1.5)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
			Substantial	71		1.4 (1.0-1.9)		
			Females					
			Unexposed and low[d]	–	–	Ref	–	
			Medium	21		1.8 (1.0-3.0)		
			High	16		1.0 (0.6-1.9)		
			Substantial	3		0.7 (0.2-2.5)		
			JTEM by PCE Exposure Index					
			Males					
			Unexposed and low[d]	–	–	Ref	–	
			Medium	37		1.0 (0.7-1.5)		
			High	47		1.2 (0.8-1.7)		
			Substantial	22		**1.8 (1.1-3.1)**		
Zheng *et al.* (2002)	Inc	OR	**Females**					Age, lifetime pack-yrs of cigarette smoking, and first degree relative with bladder cancer
			Not employed in respective occupation	–	–	Ref	–	
			Laundering and dry cleaning	3	1	9.3 (0.9-94.8)		
			Laundering and dry cleaning <10 yrs	2	0	–		
			Laundering and dry cleaning ≥10 yrs	1	1	2.1 (0.1-36.9)		
Colt *et al.* (2004)	Inc	OR	**Males**					Age, sex, and smoking status
			Never employed in respective occupation	–	–	Ref	–	
			Dry cleaning and laundry service	5	5	< 1.3 (–)		
Gaertner *et al.* (2004)	Inc	OR	Never employed in respective occupation	–	–	Ref	–	Province, race, age, smoking status, consumption of coffee, fried foods, and fruit, and employment in seven occupations: printers, rubber workers, metal workers, truck drivers, painters, hairdressers, mechanics and machinists.
			Ever dry cleaner	4	5	1.24 (0.23-6.64)		
Lynge *et al.* (2006)	Inc	RR	**Type of Work**				–	Country, sex, age group, and calendar period, and alcohol consumption, smoking status (Norway and Sweden)
			Unexposed laundry workers and persons not working in dry cleaning	–	–	Ref		
			Dry-cleaner-all 4 countries	93	292	**1.44 (1.07-1.93)**		
			Other in dry-cleaning-all 4 countries	12	52	1.08 (0.55-2.11)		
			Unclassifiable-all 4 countries	57	234	1.24 (0.83-1.83)		
			Dry-cleaner-Denmark & Norway only	62	173	**1.69 (1.18-2.43)**		
			Other in dry-cleaning-Denmark & Norway only	7	38	1.13 (0.51-2.50)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
			Unclassifiable-Denmark & Norway only	0	3	–		
			Dry Cleaners, Owners of Dry-cleaning Shops, and Others Employed in Dry-cleaning Shops with <10 Workers					
			Unexposed laundry workers and persons not working in dry cleaning	–	–	Ref	–	
			All	93	292	**1.44 (1.07-1.93)**		
			Employment duration					
			Unexposed laundry workers and persons not working in dry cleaning	–	–	Ref	–	
			0-1 yr	6	17	1.50 (0.57-3.96)		
			2-4 yrs	10	21	**2.39 (1.09-5.22)**		
			5-9 yrs	17	80	0.91 (0.52-1.59)		
			≥10 yrs	53	135	**1.57 (1.07-2.29)**		
			Unknown	6	14	1.97 (0.64-6.05)		
Reulen *et al.* (2007)	Inc	OR	Never worked in respective occupation	–	–	Ref	–	Age, sex, smoking, and education
			Textile garment workers	9	22	1.6 (0.6-4.1)		
			Building finishers and related trades workers	15	12	1.9 (0.8-4.5)		
			Metal, machinery and related trades workers	37	54	1 (0.6-1.7)		
			Machinery mechanics and fitters	13	25	0.7 (0.3-1.4)		
			Metal trades workers	15	17	1.2 (0.6-2.8)		
			Automobile Mechanics	5	10	0.6 (0.2-1.9)		
			Industrial machinery mechanics	8	16	0.7 (0.3-1.7)		
			Machine operators and assemblers	17	40	0.6 (0.3-1.2)		
			Mechanical machinery assemblers	4	18	0.3 (0.1-1.1)		
			Domestic helpers, cleaners and launderers	14	20	**2.7 (1.1-6.6)**		
Dryson *et al.* (2008)	Inc	OR	Textile bleaching, dyeing and cleaning machine operators[e,f]	3	10	0.81 (0.19-3.54)	–	Age, gender, Maori ethnicity, smoking status, and SES
Colt *et al.* (2011)	Inc	OR	**Employment in Occupation or Industry**					Age at diagnosis or control selection, sex, state, race, Hispanic ethnicity, smoking status, employment in other high-risk occupations
			Laundering and dry-cleaning machine operators and tenders					
			Never	–	–	Ref	–	
			Males	5	0	–		
			Females	1	2	0.45 (0.03-7.46)		
			Laundry, cleaning, and garment services					
			Never	–	–	Ref		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
			Males	14	14	0.91 (0.41-2.03)		
			Females	10	6	1.50 (0.50-4.50)		
			Power laundries, family and commercial					
			Never	–	–	Ref		
			Males	4	5	0.74 (0.18-2.98)		
			Females	1	4	0.30 (0.03-3.02)		
			Dry-cleaning plants, except rug					
			Never	–	–	Ref		
			Males	4	4	0.86 (0.19-3.81)		
			Females	6	2	2.19 (0.41-11.85)		
Christensen *et al.* (2013)	Inc	OR	Never exposed chlorinated solvents	372	Population: 403 Cancer: 1398	Ref	–	Smoking status; age; income; level of education; ethnicity; questionnaire type (self-reported *vs.* proxy); coffee intake, and aromatic amines exposure
			Any PCE exposure	2	Population: 4 Cancer: 32	0.3 (0.1-1.4)		
			Substantial PCE exposure	2	Population: 2 Cancer: 20	0.5 (0.1-2.5)		
Hadkhale *et al.* (2017)	Inc	HR	**All Participants, Cumulative Exposure (ppm) - 10 Yr Lag[g]**					Age, sex, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			Unexposed	–	–	Ref	0.10	
			<13.60	747	3,560	1.00 (0.92-1.09)		
			13.60-87.55	660	2,783	**1.12 (1.02-1.23)**		
			>87.55	159	702	0.94 (0.73-122)		
			<50 Yrs, Cumulative Exposure (ppm) - 10 Yr Lag[g]					Sex, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			Unexposed	–	–	Ref	0.98	
			<13.60	200	896	1.02 (0.90-1.21)		
			13.60-87.55	337	1,390	1.11 (1.00-1.30)		
			>87.55	68	327	0.90 (0.60-1.30)		
			≥50 yrs, Cumulative Exposure (ppm) - 10 Yr Lag[g]					
			Unexposed	–	–	Ref	0.07	
			<13.60	547	2,664	1.00 (0.90-1.11)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	*p*-trend	Variables Controlled
			13.60-87.55	323	1,393	1.13 (1.00-1.30)		
			>87.55	91	375	1.00 (0.70-1.38)		
			Male, Cumulative Exposure (ppm) - 10 Yr Lag[g]					Age, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, benzene, and other organic solvents)
			Unexposed	–	–	Ref	0.05	
			<13.60	639	3,099	1.00 (0.90-1.09)		
			13.60-87.55	516	2,274	1.07 (1.00-1.20)		
			>87.55	66	255	1.09 (0.30-1.53)		
			Females, Cumulative Exposure (ppm) - 10 Yr Lag[g]					
			Unexposed	–	–	Ref	0.48	
			<13.60 ppm	108	461	1.13 (0.90-1.50)		
			13.60-87.55	144	509	1.30 (1.00-1.71)		
			>87.55	93	447	0.90 (0.51-1.53)		

Notes:
CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; NR = Not Relevant; OR = Odds Ratio; PPM = Parts Per Million; RR = Risk Ratio; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Smith *et al.* (1985) analyzed bladder cancer risk by duration of employment stratified by smoking status, sex, and age, and reported "risk of disease increased significantly in association with smoking, with little effect from age and none from occupational exposure."
(b) "For each occupation or industry, the reference (unexposed) group consisted of all those who did not work in that occupation or industry" (Siemiatycki *et al.*, 1994).
(c) Unexposed defined as occupations or industries "with the least potential for exposure to carcinogenic agents" (Burns and Swanson, 1991; Swanson and Burns 1995).
(d) Pesch *et al.* (2000b) defined four exposure categories corresponding to the low, medium, high, and substantial exposure indices "using the 30th, 60th, and 90th percentiles of the distribution of the exposure variable among the exposed controls."
(e) All exposed cases were male and all exposed non-cases were female (Dryson *et al.*, 2008).
(f) Sensitivity analyses were conducted to examine if an occupation was associated with increased risk for duration (1-2 yrs, 2-10 yrs, >10 yrs). No consistent patterns for duration of employment were noted and numbers were relatively small (Dryson *et al.*, 2008).
(g) Hadkhale *et al.* (2017) noted running models with no lag and a 20-yr lag, but did not report the results.

Table F.5 PCE and Bladder Cancer Meta-analyses and Pooled Study Results

Citation	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Metric	Risk Estimate (95% CI)
Kogevinas *et al.* (2003)	Pooled	Inc	Bladder	11	Case-control	Unconditional logistic regression	Launderers, dry-cleaners and pressers	OR	1.24 (0.67-2.31)
							Textile workers		1.05 (0.81-1.36)
Reulen *et al.* (2008)	Meta-analysis	Inc	Bladder	14[a]	Cohort & case-control	Random effects	**Launderers[b]**		
							Overall	SRR	1.27 (0.95-1.71)
							Men		1.08 (0.81-1.44)
							Women		1.33 (0.61-2.90)
							Case-Control[c]		**1.66 (1.23-2.24)**
							Cohort[c]		0.82 (0.54-1.25)
							Adjusted for smoking[c]		**1.72 (1.25-2.37)**
Vlaanderen *et al.* (2014)	Meta-analysis	Inc & Mort	Bladder	3	Cohort & case-control	Random effects	**PCE Exposed Workers**		
							Including JEM results from Pesch *et al.* (2000)	RR	1.08 (0.82-1.42)
							Including JTEM results from Pesch *et al.* (2000)		1.05 (0.76-1.47)
				13			**Laundry and Dry-Cleaning Workers**		
							Cohort & case-control	RR	**1.20 (1.06- 1.36)**
				3	Cohort		Cohort studies		1.17 (0.95-1.44)
				11	Case-control		Case-control studies		**1.54 (1.17-2.04)**
Sciannameo *et al.* (2018)	Pooled	Inc	Bladder	2	Case-control	Logistic regression	Never exposed	OR	Ref
							Ever exposed		1.04 (0.56-1.91)
							Cumulative Exposure Level		
							None	OR	Ref
							< Median		1.4 (0.62-3.16)
							≥ Median		0.79 (0.31-1.97)

Notes:
CI = Confidence Interval; Inc = Incidence; ISCO= International Standard Classification of Occupations; JEM = Job Exposure Matrix; JTEM = Job Task Exposure Matrix; Mort = Mortality; NEC = Not Otherwise Classified; OR = Odds Ratio; PCE = Perchloroethylene; Ref = Reference; RR = Relative Risk; SRR= Summary Relative Risk.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Reulen *et al.* (2008) included 14 studies that evaluated PCE and bladder cancer in launderers, but not all subanalyses included all 14 studies.
(b) Results stratified by period of study were similar to overall results and none were statistically significant (Reulen *et al.*, 2008).
(c) Test of heterogeneity was statistically significant (Reulen *et al.*, 2008).

Attachment G

PCE Toxicity Studies

List of Tables

Table G.1 PCE and Bladder Cancer Chronic Oral Study Results

Table G.2 PCE and Bladder Cancer Chronic Inhalation Study Results

Table G.3 PCE and Bladder Cancer Chronic Toxicity Study Quality Overview

Table G.4 PCE and Bladder Cancer Chronic Toxicology Study Quality Assessment

Table G.1 PCE and Bladder Cancer Chronic Oral Study Results

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
NCI (1977)[a, b]	Osborne-Mendel rats	78	110	20 M	0	0/20	0/20
				50 M	471	0/50	0/50
					941	0/50	0/50
				20 F	0	0/20	0/20
				50 F	474	0/50	0/50
					949	0/50	0/50
	B6C3F1 mice		90	20 M	0	0/20	0/20
				50 M	536	0/49	0/49
					1,072	0/47	0/47
				20 F	0	0/20	0/20
				50 F	386	0/48	0/48
					772	0/48	0/48

Notes:
F = Female; M = Male; NCI = National Cancer Institute; PCE = Perchloroethylene.
(a) NCI (1977) concluded: "No significant increase in tumor incidence was observed among rats treated with tetrachloroethylene, but because of a high rate of early deaths in treated rats the results of this bioassay do not allow an evaluation of the carcinogenicity of this compound."
(b) In NCI (1977), I used the number of animals necropsied when the denominators for incidences were not specified.

Table G.2 PCE and Bladder Cancer Chronic Inhalation Study Results

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period	Treatment Groups (n, sex)	Concentration (ppm)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
NTP (1986b)[a, b]	F344/N rats	104	112-113	50 M	0	1/46	0/46
					200	0/48	0/48
					400	0/48	0/48
				50 F	0	0/47	0/47
					200	0/44	0/44
					400	1/46	1/46
	$B6C3F_1$ mice			50 M	0	0/49	0/49
					100	0/50	0/50
					200	0/50	0/50
				50 F	0	0/48	0/48
					100	0/50	0/50
					200	0/50	0/50
JISA (1993)[b]	Fischer rats	104	110-111	50 M	0	0/50	0/50
					50	0/50	0/50
					200	0/50	0/50
					600	0/50	0/50
				50 F	0	0/50	0/50
					50	0/50	0/50
					200	0/50	0/50
					600	0/50	0/50
	Crj:BDF_1 mice			50 M	0	0/50	0/50
					10	0/50	0/50
					50	0/50	0/50
					250	0/50	0/50
				50 F	0	0/50	0/50
					10	0/50	0/50
					50	0/50	0/50
					250	0/50	0/50

Notes:
F = Female; JISA = Japan Industrial Safety Association; M = Male; NTP = National Toxicology Program; PCE = Perchloroethylene; ppm = Parts per Million.

(a) NTP (1986b) reported reduced survival in male rats at the high dose, but not in female rats at any dose. Survival was also reduced in male mice at both doses, and in females at the high dose only. In addition, NTP (1986) noted that there were several instances where rats and mice escaped from their cages in exposure chambers. NTP (1986b) said "the likelihood of transposition of mice between dose groups was determined to be remote upon detailed analysis of the documents."
(b) In NTP (1986b), I used the number of animals necropsied when the denominators for incidences were not specified.
(c) JISA (1993) reported that survival was reduced in rats and mice of both sexes in the high dose groups.

Table G.3 PCE and Bladder Cancer Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Studies reported sufficient information on the species, test article name, experimental design, exposure conditions, and outcome evaluation methods.
Allocation	Animals were randomly allocated to dose groups, except in NCI (1977).
Bias	NCI (1977) stated that study animals were housed in the same rooms as other animals exposed to volatile chemicals, and that dose adjustments were made during the study. Reduced survival, which may have been attributable to tumors, was reported in both the NTP (1986b) and JISA (1993) chronic inhalation studies. NTP (1986b) reported that survival was statistically significantly reduced in rats ($p<0.001$) and mice ($p<0.001$) of both sexes compared to controls. Also, NTP (1986b) reported that in several instances rats and mice escaped from their cages within the exposure chambers. ATSDR (2019) noted that this may have resulted in potentially small exposure aberrations. Another limitation of JISA (1993) was a high mortality of rats due to the use of maximum tolerated doses, and that JISA (1993) did not perform a statistical analysis on survival data.
Sample	The chronic studies had adequate sample sizes, with the exception of NCI (1977). The number of animals in the control groups for rats and mice ($n = 20$) were significantly less than the number of animals in the exposure groups ($n = 50$).
Chemical Administration and Characterization	All three chronic studies provided adequate information on chemical source, purity, and composition, and independently verified chemical purity or took steps to ensure reported exposure levels were accurate.
Exposure Conditions	Exposure duration was too short for rats (78 weeks) to assess carcinogenicity (NCI, 1977). Two chronic studies (NTP, 1986b; JISA, 1993) had exposure periods that were too long for mice (104 weeks).
Outcome Assessment	NCI (1977) had observation periods that were too long (90 weeks in mice, 110 weeks in rats), which is not appropriate for carcinogenicity studies (OECD, 2018). Two chronic studies (NTP, 1986b; JISA, 1993) had observation periods that were too long (110-113 weeks).

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; NCI = National Cancer Institute; NTP = National Toxicology Program.

Table G.4 PCE and Bladder Cancer Chronic Toxicology Study Quality Assessment

Citation	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
NCI (1977)	**Reporting** **Chemical Administration and Characterization** **Exposure Conditions** (mice)	**Allocation:** Did not specify whether random **Bias:** Animal husbandry inadequate; high early mortality in all rats due to testing of maximum tolerated doses **Sample:** Small sample size (controls) **Exposure Conditions:** Exposure duration too short (rats) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Chronic – Inhalation			
NTP (1986b)	**Reporting** **Allocation** **Sample** **Chemical Administration and Characterization** **Exposure Conditions** (rats)	**Bias:** Reduced survival (potentially attributable to tumors, but not bladder tumors) **Exposure Conditions:** Exposure period too long (mice) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
JISA (1993)	**Reporting** **Allocation** **Sample** **Chemical Administration and Characterization** **Exposure Conditions** (rats)	**Bias:** Reduced survival; statistical analysis of survival data not performed **Exposure Conditions:** Exposure period too long (mice) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality

Notes:
JISA = Japan Industrial Safety Association; NCI = National Cancer Institute; NTP = National Toxicology Program.

Attachment H

Benzene Epidemiology Studies

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Table H.3 Benzene and Bladder Cancer Case-control Study Characteristics

Table H.4 Benzene and Bladder Cancer Case-control Study Results

Table H.5 Benzene and Bladder Cancer Pooled Study Results

Table H.1 Benzene and Bladder Cancer Cohort Study Characteristics

Study[a]	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Wong (1987a,b)	US	Chemical workers	M	Median = 25-29	7,676	1946-1975	Job title, location of work, and uniform task approach by industrial hygienist	Mort	Bladder	Company records, SSA, DMV, and death certificates	1946-1977
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Bladder	Death certificate	1942-1980
Dagg *et al.* (1992)[a] [Wong *et al.*, 1986]	US	Oil refinery employees	M	$\bar{x}$ = 27.3 range: 11.8-79	13,397	1950-1986	Work histories from employment records and personnel tapes	Mort	Bladder	Company records, NDI, SSA, California Death Index, Equifax[b], and death certificates	1950-1986
Tsai *et al.* (1993)	US	Refinery/ petrochemical workers	M	Baseline $\bar{x}$ = 45	4,585	1910-1989	Shell Health Surveillance System and work history data	Mort	Bladder	Company records, NDI, SSA Master Beneficiary Record file	1973-1989
Honda *et al.* (1995) [Wongsrichanalai *et al.*, 1989]	US	Petroleum manufacturing plant workers	M	–	9,796	1940-1989	Work history and company's health surveillance system data	Mort	Bladder	Company records, SSA Death Master file, NDI, state DMVs, and death certificates	Salaried: 1940-1989 Hourly: 1942-1989
Collingwood *et al.* (1996) [Morgan and Wong, 1985]	US	Oil refinery workers	B	Median: 20-39	4,855	1946-1987	Job, job title, and department based on work history data	Mort	Bladder	Personnel database, PBI, NDI, SSA, and death certificates	1947-1987
Satin *et al.* (1996) [Wen *et al.*, 1983; 1984; 1986]	US	Oil refinery workers	B	–	17,844	1937-1983	Job titles and company records	Mort	Bladder and other urinary organs	Personnel annuitant record systems, DMV, SSA, and NDI	1937-1987

Study[a]	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Lynge *et al.* (1997)	Denmark, Finland, Norway, and Sweden	Service station workers	B	–	Denmark: 5,250 Finland: 1,552 Norway: 3,561 Sweden: 8,606	Denmark: 1970 Finland: 1970 Norway: 1970 Sweden: 1960 and 1970	National censuses	Inc	Bladder	Denmark: National Cancer Register Finland: Finnish Cancer Register Norway: National Cancer Register Sweden: National Cancer Register	Denmark: 1970-1987 Finland: 1971-1985 Norway: 1971-1991 Sweden: 1970-1989
Pukkala (1998)	Finland	Employees of an oil and chemical enterprise[b]	B	Median <30	Total: 9,454 M: 7,512 F: 1,942	1967-1982	Employment at the company/enterprise	Inc	Bladder	Finnish Cancer Registry	1971-1994
Bulbulyan *et al.* (1999)	Russia	Printing plant employees	F	–	3,473	Minimum 2 yrs of employment at baseline: 1979[c]	Personnel records and job group	Mort	Bladder	Death certificates from Moscow Vital Statistics Department	1979-1993
Consonni *et al.* (1999)	Italy	Oil refinery workers	M	–	1,583	1949-1982	Work history records	Mort	Bladder	Population Statistics Offices and death certificates	1949-1991
Divine *et al.* (1999) [Divine *et al.*, 1985; Divine and Barron 1986]	US	Employees at refineries, petrochemical facilities and research laboratories	B	–	Total: 28,480 White M: 24,604 Non-white M: 1,783; F: 2,093	1947-1977	Personnel separation rosters and complete work histories	Mort	Bladder	Company files, NDI, SSA, HCFA, and death certificates	1947-1993

Study[a]	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Lewis *et al.* (2000a)[d] [Hanis *et al.*, 1985a, Gamble *et al.*, 2000]	US	Active and terminated workers at three oil refineries and petrochemical facilities	B	Total cohort: $\bar{x}$ = 25.9 Bayway: $\bar{x}$ = 26.2	Total cohort: 19,075 M: 17,025 F: 2,050 Bayway: 4,643 M: 4,030 F: 613	1970-1982	Company personnel and payroll records	Mort	Bladder and other urinary organs	Company records, NDI, SSA, and death certificates	1970-1992
Wong *et al.* (2001a)	US	Employees at an oil refinery	B	–	Total: 3,328: M: 2,965 F: 363	1959-1997	Personnel records and payroll files	Mort	Bladder and other urinary organs	PBI, SSA Death Master File, NDI/NDI Plus, and death certificates	1960-1997
Wong *et al.* (2001b) [Morgan and Wong, 1984]	US	Oil refinery employees	B	Median: 20-39	Total: 7,543 M: 6,832; F: 711	1945-1997	Personnel records and payroll files	Mort	Bladder and other urinary organs	PBI, SSA Death Master File, NDI/NDI Plus, and death certificates	1946-1996
Sorahan *et al.* (2002)	UK	Oil refinery and petroleum distribution workers	M	<85	Total: 45,110 Refinery workers: 28,630 Distribution workers: 16,480	1946-1974	Work histories	Mort	Bladder	NHS Central Register, General Register Office for Scotland, and death certificates	1951-1998
Lewis *et al.* (2003) [Lewis *et al.*, 2000b]	Canada	Refinery/petrochemical workers	B	M $\bar{x}$ = 29.1 F $\bar{x}$ = 27.5	Total: 25,292 M: 17,230; F: 8,062	1964-1994	Based on location, department, function, date, and expert review	Inc & Mort	Bladder	Cases: Canadian Cancer Data Base Deaths: Canadian Mortality Data Base	1964-1994
Tsai *et al.* (2003)	US	Chemical and refinery facility workers	M	Baseline $\bar{x}$= 34.2 (includes F)	3,579	1973-1999	Shell Health Surveillance System and work history data	Mort	Bladder and other urinary organs	Company records, NDI, SSA Master Beneficiary Record file	1973-1999

Study[a]	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Huebner *et al.* (2004)[d] [Hanis *et al.*, 1985, Gamble *et al.*, 2000]	US	Employees at two oil refineries and petrochemical facilities	M	$\bar{x}$=27 (includes F)	13,182	1970-1982	Company employee health status and work history register	Mort	Bladder and other urinary organs	Benefit records, NDI, and SSA	1970-1997
Sorahan *et al.* (2005)	UK	Workers occupationally exposed to benzene	B	< 85	5,514	–	Personnel reports	Inc & Mort	Bladder	ONS and DHSS	1968-2002 (mort); 1971-2001 (inc)
Gun *et al.* (2006)	Australia	Employees of Australian Institute of Petroleum member companies[d]	M	Median: 55	M: 16,547; F: 1,356	1980-2000	Survey interviews; exposure ranking by industrial hygienists based on job code	Inc & mort	Bladder	NDI and National Cancer Statistics Clearing House	Incidence: 1981-2000 Mortality: 1980-2001
Tsai *et al.* (2007)	US	Petroleum refinery and chemical workers	M	–	9,764	1948-2003	Shell Health Surveillance System and work history data	Mort	Bladder and other urinary organs	Company records, NDI, SSA Master Beneficiary Record file	1948-2003
Koh *et al.* (2011)	South Korea	Workers in a refinery and petrochemical complex	M	20-74	8,866	Early 1960s-2007	Work history and most recent job department	Inc & mort	Bladder	Cases: Central Registry of Cancer in Korea Deaths: Korea National Statistical Office	Incidence: 1997-2005 Mortality: 1992-2007
Bove *et al.* (2014b)	US	Marines and Naval personnel at CL and CP	B	CL and CP: 20-49[e]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Bladder	SSA and NDI	1979-2008

Study[a]	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Collins *et al.*, (2015) [Bloemen *et al.*, 2004; Bond *et al.*, 1986]	US	Benzene-exposed workers	B	–	2,266	1940-2009	Job title and location	Mort	Bladder and other urinary organs	HR records, NDI, state vital statistics bureaus, death certificate	1940-2009
Linet *et al.* (2015) [Yin *et al.*, 1996]	China	NCI-CAPM cohort	B	20-29[f]	Total: 109,293 Exposed: 73,789 Unexposed: 35,504	1972-1987	Factory records and job titles	Mort	Bladder	Factory records, medical records, and death certificates	1972-1999
ATSDR (2018a)[g]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[h] Civilian Employees CL: 60-64[h] CP: ≥65[h]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Bladder	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; DHSS = Department of Health and Social Services; DMV = Department of Motor Vehicles; HR = Human Resources; M = Males; NCI-CAPM = National Cancer Institute-Chinese Academy of Preventive Medicine; NDI = National Death Index; ONS = Office of National Statistics; SSA = Social Security Administration; UK = United Kingdom; US = United States.
– = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) An information services company that provided cohort member tracing Dagg *et al.* (1992).
(b) Includes employees in clerical, technical, and blue-collar positions Pukkala (1998).
(c) Benzene was used in book binding processes in these plants until 1958 Bulbulyan *et al.* (1999).
(d) Lewis *et al.* (2000a) and Huebner *et al.* (2004) both evaluate kidney cancer risk in petroleum and chemical workers at Exxon facilities in LA, TX, and NJ. Huebner *et al.* (2004) provides the longest duration of follow up and reports results for the Baton Rouge, LA, and Baytown, TX, facilities, which I report here. I report the results from Lewis *et al.* (2000a) for participants at the Bayway, NJ, facility, and all three facilities combined, which were not reported in Huebner *et al.* (2004).
(d) Head office staff and those at facilities with less than 10 employees were excluded Gun *et al.* (2006).

(e) Median age from start to end of follow-up (Bove *et al.*, 2014b).
(f) Median age at hire Linet *et al.* (2015).
(g) Ages and population sizes are reflective of Marines, Navy, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018a).
(h) Median age at survey or death (ATSDR, 2018a).

Table H.2 Benzene and Bladder Cancer Cohort Study Results

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Wong (1987a,b)[b]	US general population	Mort	SMR	**Continuously Exposed Workers**				–	Age, sex, race, and calendar time
				All	3	2.86	1.05 (0.22-3.07)		
				Duration of exposure (yrs)					
				<5	1	–	0.65		
				5-14	0		0		
				⩾15	2		3.34		
				Cumulative exposure (ppm-mos)					
				<180	2	–	1.53		
				180-719	0		0		
				⩾720	1		1.39		
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	2	4	0.5 (0.06-1.79)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	0.9 (0.18-2.62)		
Dagg *et al.* (1992)	US general population	Mort	SMR	**Work Location**					Age, sex, race, and calendar period
				Richmond	14	–	0.81 (0.44-1.35)	–	
				El Segundo	4		0.39 (0.11-1.01)		
				Overall	18		0.65 (0.39-1.03)		
				Duration of Employment (Yrs)					
				Richmond Oil Refinery					
				<5	1	–	1.17 (0.03-6.50)	–	
				5-14	1		0.36 (0.01-2.02)		
				15-29	5		0.87 (0.28-2.03)		
				≥ 30	7		0.87 (0.35-1.79)		
				El Segundo Oil Refinery					
				<5	0	–	– (0-4.74)	–	
				5-14	0		– (0-2.63)		
				15-29	1		0.28 (0.01-1.56)		
				≥ 30	3		0.68 (0.14-2.00)		
				Time Since Hire (Yrs)					
				Richmond Oil Refinery					
				<10	0	–	– (0-11.07)	–	

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Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				10-19	0		– (0-2.97)		
				20-29	2		0.65 (0.08-2.35)		
				≥ 30	12		0.94 (0.49-1.65)		
				El Segundo Oil Refinery					
				<10	0	–	– (0-18.80)	–	
				10-19	0		– (0-5.34)		
				20-29	0		– (0-2.08)		
				≥ 30	4		0.53 (0.15-1.37)		
				Hire Date					
				Richmond Oil Refinery					
				≤ 1948	13	–	0.83 (0.44-1.42)	–	
				> 1948	1		0.57 (0.01-3.15)		
				El Segundo Oil Refinery					
				≤ 1948	4	–	0.45 (0.12-1.15)	–	
				> 1948	0		–		
Tsai *et al.* (1993)	California general population	Mort	SMR	**Location**					Age, sex, race, calendar period
				Martinez location	5	–	1.02 (0.33-2.37)	–	
				Wilmington location	6		1.42 (0.52-3.09)		
				Locations combined	11		1.20 (0.60-2.15)		
Honda *et al.* (1995)	US white male population	Mort	SMR	Overall[c]	26	–	0.86 (0.56-1.26)	–	Age, sex, race, and calendar period
				Ever hourly	22		0.83 (0.52-1.26)		
Collingwood *et al.* (1996)	US general population	Mort	SMR	Overall	10	12.4	0.81 (0.39-1.48)	–	Age, sex, race, and calendar period
				White Males					
				All	9	11.6	0.78 (0.36-1.48)	–	
				Duration employment (yrs)					
				<20	2	–	0.97 (0.12-3.52)	–	
				20-29	1		0.34 (0.01-1.92)		
				30+	6		0.91 (0.33-1.98)		
				Duration since first employment (yrs)					
				<20	0	–	0 (–)	–	
				20-29	0		0 (–)		
				30+	9		0.96 (0.44-1.83)		

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Satin *et al.* (1996)	US general population	Mort	SMR	Overall	25	44.7	**0.559 (0.362-0.825)**	–	Age
	Texas general population					34.8	0.719 (0.465-1.061)		
				White men	17	–	0.645 (0.376-1.032)	–	
				Non-white men	7	–	0.903 (0.363-1.861)		
				White women	1	–	1.659 (0.041-9.245)		
				Length of Employment (Yrs)					
				<1	3	–	0.596 (–)	–	
				1-9	5		1.113 (–)		
				10-19	2		0.523 (–)		
				20-29	4		0.644 (–)		
				30+	11		0.723 (–)		
				Yrs since Hired					
				<10	1	–	2.321 (–)	–	
				10-19	1		0.554 (–)		
				20-29	2		0.377 (–)		
				30-39	5		0.503 (–)		
				40+	16		0.924 (–)		
				Period of Hire					
				<1940	20	–	0.894 (–)	–	
				1940-1945	4		0.405 (–)		
				>1945	1		0.395 (–)		
				Pay Status					
				Hourly	22	–	0.752 (–)	–	
				25-75% Salaried	2		0.787 (–)		
				90-100% Salaried	1		0.370 (–)		
Lynge et al. (1997)	Danish, Finnish, Norwegian, and Swedish general populations	Inc	SIR	Males	86	79.10	1.1 (0.9-1.3)	–	Age and sex
				Females	2	3.78	0.5 (0.0-1.9)	–	
Pukkala (1998)	Finish general population	Inc	SIR	All employees	11	13	0.82 (0.41-1.47)	–	Age, and calendar period
Bulbulyan *et al.* (1999)	Moscow general population (1992 rates)	Mort	SMR	All printing plant employees	3	1.4	2.2 (0.5-6.3)	–	Age and sex
				Compositors	0	0.1	–		
				Press operators	2	0.2	**12.5 (1.5-45.1)**		

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				Bookbinders	1	0.5	–		
Consonni *et al.* (1999)	Italian general (1949-1968) and Lombardy region populations (1969-1991)	Mort	SMR	All workers	3	4.5	0.67 (0.14-1.97)	–	Age, sex, and calendar year
Divine *et al.* (1999)	US general population	Mort	SMR	Non-white men	2	–	1.00 (0.11-3.60)	–	Age, sex, and race
				Women	2		1.95 (0.22-7.06)		
				White Men					
				All	63	–	0.83 (0.64-1.07)	–	
				Duration of employment (yrs)					
				<10	4	–	1.08 (0.29-2.77)	–	
				10-19	6		0.71 (0.26-1.55)		
				20-29	13		0.71 (0.38-1.22)		
				>30	40		0.88 (0.63-1.20)		
				Period of employment					
				<1950	55	–	0.83 (0.62-1.08)	–	
				>1950	8		0.88 (0.38-1.73)		
				Job and process unit employed >5 Yrs					
				Office; professional, supervisor	24	–	0.97 (0.62-1.44)	–	
				Controlmen, operators	30		0.95 (0.64-1.35)		
				Craft, maintenance	21		0.77 (0.48-1.18)		
				Laboratory	5		0.69 (0.22-1.61)		
				Fluid catalytic cracking	1		0.21 (0 -1.19)		
				Pipefitter, boilermaker	6		0.80 (0.29-1.75)		
				Crude stills	6		0.83 (0.30-1.80)		
				Motor oil	5		1.70 (0.55-3.96)		
Lewis *et al.* (2000a)[d]	US male general population	Mort	SMR	Total cohort	26	27.5	0.94 (0.62-1.38)	–	Age, sex, race, and calendar yr
	NJ male general population			Bayway, NJ facility employees	8	6.6	1.22 (0.53-2.41)		
Wong *et al.* (2001a)	US general population	Mort	SMR	Total cohort	2	5.73	0.349 (0.042-1.260)	–	Age, sex, race, and calendar period
				Males					
				Male employees	2	5.69	0.352 (0.043-1.271)	–	
				Duration of employment (yrs)					
				<10	1	–	1.228	–	

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				10-29	1		0.279		
				30+	1		0.0		
				Time since first employment (Yrs)					
				<20	0	–	0.0	–	
				20-39	1		0.382		
				40+	1		0.375		
				Job category					
				Maintenance	1	2.03	0.493 (0.012-2.745)	–	
				Process	0	1.75	0.0 (0.0-2.111)		
Wong *et al.* (2001b)	US general population	Mort	SMR	Total cohort	14	23.65	**0.592 (0.324-0.993)**	–	Age, sex, race, and calendar period
				Male employees	14	23.32	0.60 (0.328-1.007)		
				Female employees	0	0.33	0.0 (0.0-11.246)		
				Duration of Employment (Yrs): Male Employees					
				<10	0	–	0.0	–	
				10-29	6		0.869		
				30+	8		0.565		
				Time Since First Employment (Yrs): Male Employees					
				<20	0	–	0.0	–	
				20-39	6		0.726		
				40+	8		0.583		
				Duration of Employment (Yrs): Male Maintenance Employees					
				<10	1	–	0.350	–	
				10-29	1		0.192		
				30+	2		0.485		
				Overall	4		**0.328**		
				Duration of Employment (Yrs): Male Process Employees					
				<10	2	–	0.883	–	
				10-29	4		0.916		
				30+	1		0.352		
				Overall	7		0.739		
Sorahan *et al.* (2002)	UK general population	Mort	SMR	Refinery workers	113	112.8	1.00 (0.83-1.20)	–	Age, sex, calendar period, and country
				Distribution workers	68	68.1	1.00 (0.78-1.27)		

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Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Lewis *et al.* (2003)[e]	Canadian general population	Inc	SIR	Males	18	19.52	0.92 (0.55-1.46)	–	Age, sex, and calendar period
				Females	2	2.75	–		
				Yrs of Employment (Males)					
				<10	9	7.82	1.15 (0.53-2.18)	–	
				≥ 10- <20	5	4.96	1.01 (0.33-2.35)		
				≥ 20	1	1.62	–		
		Mort	SMR	Males	2	2.30			
				Females	0	0.32			
Tsai *et al.* (2003)	US general population	Mort	SMR	Male employees	5	5.1	0.99 (0.32-2.31)	–	Age, sex, race, calendar time
				≥10 yrs of employment					
				Male employees	5	4.9	1.01	–	
	Louisiana general population				4.6	1.09	–		
	Louisiana general population				5.0	0.99	–		
Huebner *et al.* (2004)[d]	Louisiana and Texas general populations	Mort	SMR	**Work Location**					Age, sex, race, and calendar period
				Baton Rouge	15	14.24	1.05 (0.59-1.74)	–	
				Baytown	9	11.95	0.75 (0.34-1.43)		
				Hired <1950					
				Baton Rouge	14	12.68	1.10 (0.60-1.85)	–	
				Baytown	9	10.58	0.85 (0.39-1.62)		
				Hired ⩾1950					
				Baton Rouge	1	1.56	–	–	
				Baytown	0	1.37			
Sorahan *et al.* (2005)	England and Wales general population	Mort	SMR	Exposed workers	27	26.9	1.00 (0.66-1.46)	–	Age, sex, and calendar year
		Inc	SIR	Exposed workers	69	66.6	1.04 (0.81-1.31)		
Gun *et al.* (2006)	Australian general population	Inc	SIR	Males[f]	60	51.4	1.17 (0.89-1.50)[g]	–	Age, sex, and calendar period
		Mort	SMR	Males	9	11.1	0.81 (0.37-1.53)		
Tsai *et al.* (2007)	County general population	Mort	SMR	**Work Location**					Age, sex, race, calendar period
				Refinery	14	–	0.86 (0.47-1.45)	–	
				Chemical	6		0.62 (0.23-1.36)		
				Total	20		0.77 (0.47-1.20)		

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				Period of Hire					
				<1950	15	–	0.82 (0.46-1.36)	–	
				1950-1959	3		0.50 (0.10-1.45)		
				≥ 1960	2		1.28 (0.16-4.64)		
				Worked for ≥10 yrs, by Location					
				Refinery	13	–	1.01 (0.54-1.73)	–	
				Chemical	3		0.47 (0.10-1.36)		
				Total	16		0.83 (0.47-1.35)		
Koh *et al.* (2011)	South Korean general population	Inc	SIR	All workers	6	–	1.83 (0.67-3.99)	–	Age, sex, and calendar period
				Manufacturing workers	4		1.75 (0.48-4.47)		
				Office workers	2		2.04 (0.25-7.36)		
				Job Classification					
				Product workers	4	–	2.77 (0.76-7.10)	–	
				Maintenance workers	0		– (0-4.97)		
				Laboratory workers	0		– (0-12.24)		
				Office workers	2		2.04 (0.25-7.36)		
		Mort	SMR	All workers	0	–	– (0-4.78)	–	
				Manufacturing workers	0		– (0-7.01)		
				Office workers	0		– (0-15.04)		
				Job Classification					
				Product workers	0	–	– (0-11)	–	
				Maintenance workers	0		– (0-26.70)		
				Laboratory workers	0		– (0-70.50)		
				Office workers	0		– (0-15)		
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-45)[h]	3	–	0.52 (0.15-1.85)	–	
				Medium/high (>45-601)[h]	8		1.07 (0.44-2.60)		
	CL Marines & Navy personnel with exposure <2 µg/L-mos[i]			Low (2-45)	0		0.00		
				Medium (>45-110)	5		4.04 (0.77-21.18)		
				High (>110-601)	3		2.26 (0.37-13.78)		
Collins *et al.* (2015)	US general population	Mort	SMR	Overall	11	–	0.84 (0.42–1.51)	–	Age, sex, race, and year

Citation	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
				> 30-yrs since first benzene exposure	11	–	1.04 (0.52–1.86)	–	
Linet *et al.* (2015)	Benzene unexposed workers	Mort	RR	Benzene exposed workers	18	73,771	0.9 (0.4-2.2)	–	Age, sex, and calendar year
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy personnel**					Age and sex
				Cumulative exposure level[j,k]					
				Low	88	–	1.28 (0.76-2.15)	–	
				Medium	83		1.68 (1.00-2.82)		
				High	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure[j]			Medium	83		1.34 (0.98-1.85)		
				High	11		0.74 (0.39-1.43)		

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; LA = Louisiana; Mort = Mortality; Mos = months; NJ = New Jersey; OR = Odds Ratio; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; TX = Texas; µg/L = Micrograms per Liter; US = United States; VC = Vinyl Chloride; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Results for all continuously exposed workers were reported in Wong (1987a) and cumulative and duration of exposure results were reported in Wong (1987b). Analyses considering employees with intermittent exposures had similar results to those reported for employees with continuous exposures (Wong 1987a,b). Wong (1987b) reported no associations between benzene exposure and bladder cancer based on category of max peak exposure (*i.e.*, <25, 25-100, or >100 ppm) or when accounting for latency (*i.e.*, <10, 10-19, or ⩾20 yrs).
(c) Included salaried workers who had a longer follow-up time than hourly workers (Honda *et al.*, 1995).
(d) Lewis *et al.* (2000a) and Huebner *et al.* (2004) both evaluate bladder and other urinary organ cancer risk in petroleum and chemical workers at Exxon facilities in LA, TX, and NJ. Huebner *et al.* (2004) provides the longest duration of follow up and reports results for the Baton Rouge, LA, and Baytown, TX, facilities, which I report here. I report the results from Lewis *et al.* (2000a) for participants at the Bayway, NJ, facility, and all three facilities combined, which were not reported in Huebner *et al.* (2004).
(e) Unless the SMR is statistically significant, when the number of cases/deaths <5, the SIR/SMR and 95% CI are not presented (Lewis *et al.*, 2003).
(f) Two bladder cancer cases were reported in women. No effect estimates were provided (Gun *et al.*, 2006).
(g) Bladder cancer did not occur in significant excess in any workplace type and there was no trend in incidence with period of first employment, duration of employment, or time since hire; nor was there any trend in incidence with hydrocarbon exposure ranking (Gun *et al.*, 2006).

(h) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014b). I report the values consistent with the text definition.
(i) To evaluate exposure-response relationships, the authors evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al*., 2014b).
(j) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).
(k) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018a).

Table H.3 Benzene and Bladder Cancer Case-control Study Characteristics

Citation	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (years)	Cases		Controls		
							N	Source	N	Source	
Steineck *et al.* (1990)	Sweden	Inc	Urothelial	1985-1987[a]	M	40-74	254	Cancer registry and urological departments	287	Stockholm population register	Interview, self-reported job history
Greenland *et al.* (1994)[b]	US	Mort	Bladder	1969-1984	M	21-90	512	Employee pension records	1,202	Workers at same transformer-manufacturing facility	Job history records and JEM
Gérin *et al.* (1998)	Canada	Inc	Bladder	1979-1986	M	35-70	3,730	Local hospital records	Population: 533 Cancer: 533	Local electoral lists	Interviews, self-reported job history, and expert opinion
Pesch *et al.* (2000)	Germany	Inc	Urothelial	1991-1995	B	63-76 (median)	1,035	Hospitals in the study areas	4,298	Local residency registries	Interview, self-reported job history, JEM
Hadkhale *et al.* (2017)	Finland, Iceland, Norway, and Sweden	Inc	Bladder	1961-2005	B[c]	20-65[d]	113,343	NOCCA	566,715	NOCCA	Occupational codes and NOCCA-JEM
Shala *et al.* (2023)	Norway	Inc	Bladder[e]	1999-2017	M[f]	Median at baseline: 54 Range at first employment: 15-67	189	Offshore petroleum workers	2,065	Offshore petroleum workers	JEM based on work history and job categories

Notes:
B = Both Males and Females; JEM = Job-Exposure Matrix; M = Males; NOCCA = Nordic Occupational Cancer Database; US = United States; Yrs = Years.
– = Not Reported.
(a) Some analyses ignored exposures after 1981 (Steineck *et al.*, 1990).
(b) Restricted to white males (Greenland *et al.*, 1994).
(c) Approximately 95% male (Hadkhale *et al.*, 2017).
(d) Hadkhale *et al.* (2017) stated, "Exposure was assumed to start at the age of 20 years and end at the index date or at 65 years, whichever occurred first."
(e) Over 95% of cases were urothelial carcinomas (Shala *et al.*, 2023).
(f) Restricted to males because only six bladder cancer cases were diagnosed among women and 68% of women worked in catering and administration with low hydrocarbon exposure (Shala *et al.*, 2023).

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Table H.4 Benzene and Bladder Cancer Case-control Study Results

Citation	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
Steineck *et al.* (1990)	Inc	RR[a]	**Urothelial Cancer**					Age and smoking status
			Unexposed	–	–	Ref	–	
			Ever exposed[b]	26	16	2.0 (1.0-3.8)		
			Annual dose[b]					
			Unexposed	–	–	Ref		
			Low	9	6	1.7 (0.6-5.1)		
			Moderate	4	5	1.1 (0.3-4.5)		
			High	13	5	3.0 (1.0-8.7)		
			Duration of exposure					
			< 1	–	–	Ref		
			1-9 years	13	9	1.8 (0.7-4.5)		
			10 + years	13	7	2.2 (0.8-5.7)		
			Year of first exposure[c]					
			Before 1942	8	5	2.0 (0.6-6.5)		
			1942-1961	15	8	2.3 (0-.9-5.8)		
			1962-1981	3	3	1.0 (0.2-5.3)		
Greenland *et al.* (1994)[d]	Mort	OR	No Exposure	–	–	Ref	–	Age and year of death
			Any exposure	–	–	1.02 (0.29-3.51)		
Gérin *et al.* (1998)[e]	Inc	OR	**Cumulative Exposure**					Age, family income, ethnicity, smoking, and respondent status (self or proxy)
			Unexposed	395	860	Ref	–	
			Low	65	143	1.0 (0.7-1.3)		
			Medium	22	37	1.2 (0.7-2.0)		
			High	2	26	**0.2 (0.0-0.6)**		
Pesch *et al.* (2000)	Inc	OR	**British JEM by benzene exposure index**					Age, study center, smoking status
			Males					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	95	–	1.1 (0.8-1.4)		
			High	70	–	0.9 (0.7-1.2)		
			Substantial	47	–	1.5 (1.0-2.1)		
			Females					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	21	–	1.2 (0.7-2.0)		

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Citation	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			High	18	–	1.5 (0.9-2.8)		
			Substantial	8	–	1.4 (0.6-3.3)		
			German JEM by benzene exposure index					
			Males					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	177	–	1.1 (0.9-1.3)		
			High	169	–	1.2 (1.0-1.6)		
			Substantial	68	–	1.2 (0.8-1.6)		
			Females					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	27	–	1.0 (0.7-1.7)		
			High	23	–	0.8 (0.5-1.4)		
			Substantial	5	–	0.6 (0.2-1.6)		
			Job-task exposure matrix, by benzene exposure index					
			Males					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	51	–	0.7 (0.5-1.0)		
			High	71	–	1.0 (0.7-1.3)		
			Substantial	37	–	1.4 (0.9-2.1)		
			Females					
			Unexposed and low[f]	–	–	Ref	–	
			Medium	2	–	0.4 (0.1-1.8)		
			High	3	–	0.4 (0.1-1.2)		
			Substantial	2	–	0.8 (0.2-3.7)		
Hadkhale *et al.* (2017)[g]	Inc	HR	**All Participants, Cumulative Exposure (ppm) with 10 yr lag[h]**					Age, sex, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, and other exposures (aromatic hydrocarbon solvents, toluene, chlorinated hydrocarbon solvents,
			Unexposed	–	–	Ref	0.07	
			<5.68	3,953	18,167	1.00 (0.92-1.08)		
			5.68-15.04	3,172	14,510	1.05 (1.00-1.15)		
			>15.04	855	3,560	**1.16 (1.04-1.31)**		
			Participants <50 yrs., Cumulative Exposure (ppm)[h] with 10 yr lag[h]					
			Unexposed	–	–	Ref	0.10	
			<5.68	1,191	5,297	1.00 (0.90-1.20)		
			5.68-15.04	1,568	7,036	1.07 (0.93-1.24)		

Citation	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			>15.04	649	2,595	**1.22 (1.03-1.44)**		perchloroethylene, 1,1,1 trichloroethane, trichloroethylene and other organic solvents)
			Participants ≥50 years, Cumulative Exposure (ppm)[h] with 10 yr lag[h]					
			Unexposed	–	–	Ref	0.96	
			<5.68	2,762	12,870	1.00 (0.90-1.09)		
			5.68-15.04	1,604	7,474	1.04 (0.92-1.20)		
			>15.04	206	965	1.04 (0.90-1.26)		
Shala *et al.* (2023)	Inc	HR	Never exposed	49	631	Ref	–	Age, yr of first employment, smoking and education[i]
			Ever exposed	140	1,434	1.25 (0.89-1.77)[g]		
			Duration of exposure (Yrs)					
			0	49	631	Ref.	**0.044**	
			>0-<5.5	46	481	1.18 (0.77-1.83)		
			5.5-<13.3	28	485	1.03 (0.66-1.60)		
			13.3-<18.8	23	239	1.32 (0.77-2.27)		
			18.8-33.5	33	229	**1.89 (1.14-3.13)**		
			Per yr increase	189	2,065	1.02 (1.00-1.04)	–	
			Average intensity (Cumulative Exposure/Duration of exposure [Yrs])					
			0	49	631	Ref	0.160	
			>0-0.5	79	825	1.22 (0.84-1.79)		
			>0.5-1.0	29	312	1.11 (0.68-1.82)		
			>1	32	297	1.47 (0.91-2.37)		
			Per unit increase in average intensity	189	2,065	1.16 (0.89-1.51)	–	
			Cumulative exposure (JEM rating[h] * Duration of exposure [Yrs])					
			0	49	631	Ref	0.065	
			>0-<2.0	47	479	1.20 (0.78-1.85)		
			2.0-<7.6	38	486	1.05 (0.67-1.64)		
			7.6-<15.3	27	235	1.44 (0.86-2.41)		
			15.3-51.4	28	234	1.60 (0.97-2.63)		
			Per unit increase in cumulative exposure	189	2,065	1.02 (1.00-1.03)	–	
			Duration of exposure (Yrs) with 10 Yr Lag: Complete case analysis					Age, yr of first employment, smoking and education
			0	47	–	Ref	0.139	
			>0-<5.5	46		1.25 (0.81-1.92)		

Citation	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			5.5-<13.3	38		1.12 (0.72-1.75)		
			13.3-<18.8	24		1.40 (0.82-2.40)		
			18.8-33.5	22		1.61 (0.91-2.85)		
			Per year increase	177		1.01 (0.99-1.04)	–	
			Cumulative exposure (JEM rating[j] * Duration of exposure [Yrs]) with 10 Yr Lag: Complete case analysis					
			0	47	–	Ref.	0.141	
			>0-<2.0	45		1.24 (0.80-1.91)		
			2.0-<7.6	39		1.16 (0.74-1.81)		
			7.6-<15.3	22		1.31 (0.75-2.27)		
			15.3-51.4	24		1.56 (0.92-2.66)		
			Per unit increase in cumulative exposure	177		1.01 (1.00-1.03)	–	

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; Ref = Reference. – = Not Reported.
Bolded values indicate statistical significance.
(a) Steineck *et al.* (1990) reported RRs, but reported running a logistic regression model.
(b) Steineck *et al.* (1990) reported that "any exposure after 1981 was ignored, thus allowing for a latency period."
(c) Reference group not clearly defined for this analysis (Steineck *et al.*, 1990).
(d) Restricted to white males (Greenland *et al.*, 1994).
(e) The exposure categories were based on the likelihood of exposure, the frequency of exposure during a normal work week and the concentration of the agent in the environment (Gérin *et al.*, 1998).
(f) Pesch *et al.* (2000) defined four exposure categories corresponding to the low, medium, high, and substantial exposure indices "using the 30th, 60th, and 90th percentiles of the distribution of the exposure variable among the exposed controls."
(g) Analyses were also conducted stratified by sex. Hadkhale *et al.* (2017) reported results for males were similar to the overall population and no association in females. They noted, "We did not observe any significant interactions indicating that the dose-response trend patterns would be different in males and females."
(h) Authors reported running models with no lag and a 20-year lag, but did not report those results (Hadkhale *et al.*, 2017).
(i) Results were similar in models additionally adjusted for physical activity, BMI, work as a painter and for polycyclic aromatic hydrocarbon exposure (Shala *et al.*, 2023).
(j) Shala *et al.* (2023) defined JEM ratings as follows: unlikely exposed = 0; possibly exposed = 1; probably exposed= 2 (*i.e.*, at least 50% of the workers within the job category were exposed); and probably exposed = 3 (*i.e.*, those thought to have the highest exposure intensity).

Table H.5 Benzene and Bladder Cancer Meta-Analyses and Pooled Study Results

Citation	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Metric	Risk Estimate (95% CI)
Sciannameo *et al.* (2018)	Pooled	Inc	Bladder	2	Case-control	Logistic regression	Never exposed	OR	Ref
							Ever exposed		0.99 (0.77-1.29)
							Cumulative Exposure Level		
							None	OR	Ref
							< Median		1.08 (0.77-1.52)
							≥ Median		0.94 (0.67-1.32)
Seyyedsalehi *et al.* (2024)[a, b]	Meta-analysis	Inc & Mort	Bladder	35	Cohort & case-control	Random effects	Overall	RR	1.07 (0.97-1.18)
				5	Case-control				1.17 (0.95-1.45)
				30	Cohort				1.04 (0.92-1.19)
		Inc		17	Cohort & case-control				**1.10 (1.01-1.20)**
		Mort		23					0.99 (0.83-1.19)
		Inc & Mort		5			**Dose Category[b]**		
							Low	RR	1.19 (0.92–1.53)
				4			Medium		1.06 (0.99–1.13)
				5			High		1.20 (0.81–1.79)

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; Ref = Reference; RR = Risk Ratio.
Bolded values indicate statistical significance.
(a) Stratified analyses by geographic region, quality score, control for tobacco smoking, exposure circumstance, and sex were also reported and did not demonstrate any associations. A stratified analysis by year of publication did produce a statistically significant association for studies published in the year 2000 or later (RR = 1.11, 95% CI: 1.01-1.21), but not for studies published before 2000. Stratified analyses did not reveal any heterogeneity between study groups (Seyyedsalehi *et al.*, 2024).
(b) A significant p-value for linear trend (p=0.01) was reported (Seyyedsalehi *et al.*, 2024).

Attachment I

Benzene Toxicity Studies

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Table I.1 Benzene and Bladder Cancer Chronic Ingestion Study Results

Table I.2 Benzene and Bladder Cancer Chronic Inhalation Study Results

Table I.3 Benzene and Bladder Cancer Chronic Toxicity Study Quality Overview

Table I.4 Benzene and Bladder Cancer Chronic Study Quality Assessment

Table I.1 Benzene and Bladder Cancer Chronic Ingestion Study Results

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni *et al.* (1979, 1983, 1985, 1988b, 1989); Maltoni and Scarnato (1979)	Sprague-Dawley Rat	52	Until spontaneous death	30 M	0	NR	NR
				30 M	50	NR	NR
				35 M	250	NR	NR
				30 F	0	NR	NR
				30 F	50	NR	NR
				35 F	250	NR	NR
	Sprague-Dawley Rat	104		50 M	0	NR	NR
				40 M	500	NR	NR
				50 F	0	NR	NR
				40 F	500	NR	NR
	Wistar Rat	104		40 M	0	NR	NR
					500	NR	NR
				40 F	0	NR	NR
					500	NR	NR
	Swiss Mouse	78		40 M	0	NR	NR
					500	NR	NR
				40 F	0	NR	NR
					500	NR	NR
	RF/J Mice	52		40 M	0	NR	NR
					500	NR	NR
				40 F	0	NR	NR
					500	NR	NR

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Cancer Outcome	
						Benign Tumors	Malignant Tumors
Huff *et al.* (1989); NTP (1986a)[a]	F3344/N Rat	104	104	50 M	0	0/50	0/50
					50	0/50	0/50
					100	0/50	0/50
					200	0/50	0/50
				50 F	0	0/50	0/50
					25	0/50	0/50
					50	0/50	0/50
					100	0/50	0/50
	B6C3 Mouse			50 M	0	0/50	0/50
					25	0/50	0/50
					50	0/50	0/50
					100	0/50	0/50
				50 F	0	0/50	0/50
					25	0/50	0/50
					50	0/50	0/50
					100	0/50	0/50

Notes:
F = Female; M = Male.
NR = Bladder was analyzed, but bladder tumor findings were not reported.
(a) For Huff *et al.* (1989); NTP (1986a I used the number of animals necropsied from NTP (1986awhen the denominators for incidences were not specified.

Table I.2 Benzene and Bladder Cancer Chronic Inhalation Study Results

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Concentration (ppm)	Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni *et al.* (1982, 1985, 1983, 1989)	Sprague-Dawley Rat	104	Until spontaneous death	158 M	0	NR	NR
				75 M	200-300	NR	NR
				149 F	0	NR	NR
				60 F	0	NR	NR
				54 F	200-300	NR	NR
				65 F	200-300	NR	NR

Notes:
F = Female; M = Male.
NR = Bladder was analyzed, but bladder tumor findings were not reported.

Table I.3 Benzene and Bladder Cancer Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most studies reported information on the species; the test article name; the experimental design; the levels, duration, and route of exposure; and the Outcome Assessment methods. Maltoni *et al.* (1983, 1985, 1988b, 1989) stated that the bladder was examined but did not report any bladder tumor data.
Allocation	Animals were randomly allocated to dose groups in all studies.
Bias	There was no indication of bias due to co-exposures, vehicle, diet, palatability, husbandry, or health status in any study.
Sample	Only the Maltoni *et al.* (1982, 1985, 1983, 1989) inhalation bioassays and Huff *et al.* (1989); NTP (1986a) had adequate sample sizes. All animals were accounted for throughout each study.
Chemical Administration and Characterization	All studies took steps to ensure the exposure levels were accurate. Only Huff *et al.* (1989)/NTPa (1986) identified the benzene source and confirmed purity.
Exposure Conditions	The duration of exposure varied considerably among studies; five chronic bioassays exposed animals for 104 weeks (Maltoni *et al.*, 1982, 1983, 1985, 1988b, 1989; Huff *et al.*, 1989/NTP, 1986a), two for 52 weeks (Maltoni *et al.*, 1983, 1985, 1988b, 1989; Maltoni and Scarnato, 1979), and one for 78 weeks (Maltoni *et al.*, 1983, 1985, 1988b, 1989). A single dose was tested in four chronic oral bioassays (Maltoni *et al.*, 1983, 1985, 1988b, 1989). Three oral bioassays tested more than one dose (Maltoni *et al.*, 1983, 1985, 1988b, 1989; Maltoni and Scarnato, 1979; Huff *et al.*, 1989/NTP, 1986a).
Outcome Assessment	Maltoni *et al.* (1983, 1985, 1988b, 1989) examined animals after spontaneous death rather than after sacrifice. Gift (2013) re-analyzed the results from several oral and inhalation bioassays conducted at the Ramazzini Institute (where the Maltoni *et al.* [1983, 1985, 1988b, 1989] studies were conducted) and concluded that the proper health status of experimental animals may not have been maintained. Gift (2013) also noted that "the quality and availability of tissues for pathology slides may suffer in the RI life span protocol due to tissue autolysis."

Note:
NTP = National Toxicology Program.

Table I.4 Benzene and Bladder Cancer Chronic Study Quality Assessment

Citation	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
Maltoni *et al.* (1983, 1985, 1988b, 1989); Maltoni and Scarnato (1979)	**Allocation** **Bias**	**Reporting:** No bladder tumor data **Sample:** Small sample size **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Exposure duration too short in some bioassays; only one dose of benzene tested in all but one bioassay **Outcome Assessment:** Observation period too long	**None:** No bladder tumor data
Huff *et al.* (1989); NTP (1986a)	**Reporting** **Allocation** **Bias** **Sample** **Chemical Administration and Characterization** **Exposure Conditions** (rats) **Outcome Assessment** (rats)	**Exposure Conditions:** Exposure period too long (mice) **Outcome Assessment:** Observation period too long (mice)	**Limited:** Low study quality (mice)
Chronic – Inhalation			
Maltoni *et al.* (1982, 1985, 1983)	**Allocation** **Bias** **Sample** **Exposure Conditions**	**Reporting:** No bladder tumor data **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Outcome Assessment:** Observation period too long	**None:** No bladder tumor data

Attachment J

Vinyl Chloride Epidemiology Studies

List of Tables

Table J.1 Vinyl Chloride and Bladder Cancer Cohort Study Characteristics

Table J.2 Vinyl Chloride and Bladder Cancer Cohort Study Results

Table J.1 Vinyl Chloride and Bladder Cancer Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
Teta *et al.* (1990)	US	Hourly male employees of the Union Carbide Corporation's Chemicals and Plastics business group	M	–	7,901	1974-1983	Hourly employment for at least one year with the Chemicals and Plastics business group	Mort	Bladder	SSA, NDI, company mortality register, benefit records, and death certificates	1974-1983
Bove *et al.* (2014b)	US	Marines & Navy personnel at CL and CP	B	CL and CP: 20-49[a]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Bladder	SSA and NDI	1979-2008
Carreón *et al.* (2014) [Prince *et al.*, 2000]	US	Workers at a chemical manufacturing plant	B	Median at first employment = 23 (range: 17-65)	1,874	1946-2006	Assignment to the PVC, vinyl department <1995, jobs in shipping, packing and warehousing, rubber compounds, quality control, and research and development, jobs with assignment throughout the plant, and workers with no assigned department <1995	Mort	Bladder and other urinary organs	NDI, NDI Plus, and Florida Department of Health	1960-2007
Mundt *et al.* (2017) [Mundt *et al.*, 2000]	US	VC or PVC resin manufacturing workers	M	28[b]	9,951	1942-1972	Employment ≥1 yr at factory	Mort	Bladder and other urinary organs	NDI, death certificates	1942-2013

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Cancer Type	Ascertainment	Follow-up Period
ATSDR (2018a)[c]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[d] Civilian Employees CL: 60-64[d] CP: ≥65[d]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Bladder	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; M = Males; Mort = Mortality; NDI = National Death Index; PVC = Polyvinyl Chloride; SSA = Social Security Administration; US = United States, Yr = Year.
– = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Median age from start to end of follow-up (Bove *et al.*, 2014b).
(b) Mean age at hire (Mundt *et al.*, 2017).
(c) Ages and population sizes are reflective of Navy, Marine, and civilian respondents to the morbidity survey and do not include the 5,263 Marine, Navy, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018a).
(d) Median age at survey or death (ATSDR, 2018a).

Table J.2 Vinyl Chloride and Bladder Cancer Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases or Exposed Non-cases[a]	Risk Estimate (95% CI)	*p*-trend	Covariate Adjustment
Teta *et al.* (1990)	US white males	Mort	SMR	Hourly male employees in the Chemicals and Plastics business group	4	3.8	– (0.29-2.69)	–	Age, sex, and calendar yr
Bove *et al.* (2014b)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-205)[b]	4	–	0.75 (0.24-2.34)	–	
				Medium/high (>205-2,800)[b]	7		0.88 (0.35-2.22)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[c]			Low (>1-205)	0		0.00		
				Medium (>205-500)	5		2.59 (0.61-10.98)		
				High (>500-2,800)	2		0.91 (0.15-5.52)		
Carreón *et al.* (2014)	US general population	Mort	SMR	All Workers	4	–	1.55 (0.42-3.98)	–	Age, sex, race, and calendar yr
				Duration of Employment (Days)					
				<90	0	–	0 (0-11.58)	–	
				≥90	4		1.77 (0.48-4.54)		
Mundt *et al.* (2017)	NIOSH state-specific groups for white men	Mort	SMR	Overall	55	45.7	1.20 (0.91 to 1.57)	–	Age, sex, calendar year and plant type (VC *vs.* PVC)
ATSDR (2018a)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level[d,e]					
				Low[e]	88	–	1.28 (0.76-2.15)	–	
				Medium[e]	83		1.68 (1.00-2.82)		
				High[e]	11		0.93 (0.43-2.01)		
	CL Marines & Navy personnel with low exposure[e]			Medium[e]	83		1.34 (0.98-1.85)		
				High[e]	11		0.74 (0.39-1.43)		

Notes:

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ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; Mos = Months; NIOSH = National Institute for Occupational Safety and Health; OR = Odds Ratio; PVC = Polyvinyl Chloride; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Micrograms per Liter; US = United States; VC = Vinyl Chloride; Yrs = Years.

– = Not Reported.

Bolded values indicate statistical significance.

When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.

(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.

(b) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014b). I report the values consistent with the text definition.

(c) To evaluate exposure-response relationships, the authors evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al*., 2014b).

(d) Categorized as low exposure (<50th percentile), medium exposure (⩾50th percentile to <90th percentile), and high exposure (⩾90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018a).

(e) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018a).

Attachment K

Vinyl Chloride Toxicity Studies

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Table K.1 Vinyl Chloride and Bladder Cancer Chronic Ingestion Study Results

Table K.2 Vinyl Chloride and Bladder Cancer Chronic Inhalation Study Results

Table K.3 Vinyl Chloride and Bladder Cancer Chronic Intraperitoneal Injection Study Results

Table K.4 Vinyl Chloride and Bladder Cancer Chronic Toxicity Study Quality Overview

Table K.5 Vinyl Chloride and Bladder Cancer Chronic Toxicity Study Quality Assessment

Table K.1 Vinyl Chloride and Bladder Cancer Chronic Ingestion Study Results

Reference	Strain/ Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n, sex)	Dose (mg/kg-d)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
Feron *et al.* (1981)[a]	Wistar rats	135	M: 135 F: 144	80 M	0	0/80	0/80
				60 M	1.7	0/60	0/60
					5.0	0/60	0/60
				80 M	14.1	0/80	0/80
					300	0/80	0/80
		144		80 F	0	0/80	0/80
				60 F	1.7	0/60	0/60
					5.0	0/60	0/60
				80 F	14.1	0/80	0/80
					300	0/80	0/80
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Sprague-Dawley rats	52 - 59	Until spontaneous death	40 M	0	0/40	1/40
					3.33	1/40	0/40
					16.65	0/40	0/40
					50	0/40	0/40
				40 F	0	0/40	0/40
					3.33	0/40	0/40
					16.65	0/40	0/40
					50	0/40	0/40
	Sprague-Dawley rats			75 M	0	0/75	0/75
					0.03	0/75	0/75
					0.3	0/75	0/75
					1	0/74	0/74
				75 F	0	0/75	0/75
					0.03	0/75	0/75
					0.3	0/73	0/73
					1	0/75	0/75

Notes:
F = Female; M = Male.
NR = bladder was analyzed, but bladder tumor findings were not reported.
(a) Vinyl chloride was administered as a polyvinyl chloride powder with vinyl chloride monomer (VCM). Doses of 1.7 mg/kg-d, 5 mg/kg-d, and 14.1 mg/kg-d were administered *via* feed; the 300 mg/kg-d dose was administered *via* gavage, but there was no gavage control group. The exposure duration is the point at which 75% of the control rats were dead. The results here are for rats found dead or sacrificed in extremis or terminally (not for scheduled sacrifice at 26 or 52 weeks). An "unclassified epithelial tumor" of the urinary bladder was reported in one male rat exposed to 5 mg/kg-day VC (Feron *et al.*, 1981).
(b) I used the "corrected number of animals" as the denominators for reporting incidences of bladder tumors.

Table K.2 Vinyl Chloride and Bladder Cancer Chronic Inhalation Study Results

Citation	Strain/ Species	Exposure Duration	Observation Period	Treatment Groups (n, sex)	Dose (ppm)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Sprague-Dawley rats	52 weeks	Until spontaneous death	30 M	0	NR	NR
					50	NR	NR
					250	NR	NR
					500	NR	NR
					2,500	NR	NR
					6,000	NR	NR
					10,000	NR	NR
				30 F	0	NR	NR
					50	NR	NR
					250	NR	NR
					500	NR	NR
					2,500	NR	NR
					6,000	NR	NR
					10,000	NR	NR
	Sprague-Dawley rats	52 weeks		85 M	0	NR	NR
				60 M	100	NR	NR
					150	NR	NR
					200	NR	NR
				100 F	0	NR	NR
				60 F	100	NR	NR
					150	NR	NR
					200	NR	NR
	Sprague-Dawley rats	52 weeks		30 M	30,000	NR	NR
				30 F		NR	NR
	Wistar rats	52 weeks		40 M	0	NR	NR
				30 M	50	NR	NR
					250	NR	NR
					500	NR	NR
					2,500	NR	NR
					6,000	NR	NR
					10,000	NR	NR
	Sprague-Dawley rats	52 weeks		50 M	0	NR	NR
				150 M	50	NR	NR
				50 F	0	NR	NR
				150 F	50	NR	NR
	Sprague-Dawley rats	52 weeks		60 M	0	NR	NR
					1	NR	NR
					5	NR	NR
					10	NR	NR
					25	NR	NR
				60 F	NR	NR	NR
					NR	NR	NR
					NR	NR	NR
					NR	NR	NR

Citation	Strain/ Species	Exposure Duration	Observation Period	Treatment Groups (n, sex)	Dose (ppm)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
					NR	NR	NR
	Wistar rats	52 weeks		120-130 M	0	NR	NR
					1	NR	NR
Holmberg *et al.* (1976)	NMRI mice	52 weeks	Until moribund or spontaneous death	12 M	0	NR	NR
					50	NR	NR
				12 F	0	NR	NR
					50	NR	NR
Maltoni and Cotti (1988)[a]	Sprague-Dawley rats	76 weeks	Until spontaneous death	60 F adults	0	NR	NR
				54 F adults	2,500	NR	NR
				307 M+F embryos	0	NR	NR
				127 M+F embryos	2,500	NR	NR

Notes:
F = Female; M = Male.
NR = Bladder was analyzed, but bladder tumor findings were not reported.
(a) Adult breeders were exposed by inhalation for 76 weeks. Offspring exposed from gestational day (GD) 12 by the transplacental route and then by inhalation for 76 weeks (Maltoni and Cotti, 1988).

Table K.3 Vinyl Chloride and Bladder Cancer Chronic Intraperitoneal Injection Study Results

Citation	Strain/ Species	Exposure Duration	Observation Period	Treatment Groups (n, sex)	Dose (mg)	Bladder Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Sprague-Dawley	NR	Until spontaneous death	30 M	0	NR	0/28
		4 times at 2-month intervals			4.25	NR	1/26
		3 times at 2-month intervals				NR	0/30
		2 times at 2-month intervals				NR	0/28
		NR		30 F	0	NR	0/27
		4 times at 2-month intervals			4.25	NR	0/30
		3 times at 2-month intervals				NR	0/30
		2 times at 2-month intervals				NR	1/28

Notes:
F = Female; M = Male.
NR = Not Reported (study stated bladder was analyzed, but did not report any bladder tumor findings).

Table K.4 Vinyl Chloride and Bladder Cancer Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most bioassays reported information on the species; the test article name; the experimental design; the levels, duration, and route of exposure; and the outcome evaluation methods. The majority of studies that stated they examined the bladder did not report any data on bladder tumors. The only exception was Feron *et al.* (1981) and Maltoni and Lefemine (1975) and Maltoni *et al.* (1981, 1984) (oral exposure).
Allocation	With the exception of Feron *et al.* (1981), bioassays did not indicate whether animals were randomly allocated to experimental groups.
Bias	There was no indication of bias due to co-exposures, vehicle, diet, palatability, husbandry, or health status.
Sample	Most bioassays had adequate sample sizes; the only exceptions were Holmberg *et al.* (1976) and Maltoni and Lefemine (1975) and Maltoni *et al.* (1981, 1984) for ingestion, inhalation, and intraperitoneal exposure. All animals were accounted for in the studies by Holmberg *et al.* (1976) and Maltoni and Cotti (1988).
Chemical Administration and Characterization	Only two studies (Feron *et al.*, 1981; Maltoni and Cotti, 1988) provided adequate information on chemical source, purity, and composition; independently verified chemical purity; and took steps to ensure reported exposure levels were accurate.
Exposure Conditions	The duration of exposure was not appropriate in any study: 10 chronic bioassays exposed rats or mice for 52 weeks (Maltoni and Lefemine, 1975; Maltoni *et al.*, 1981, 1984; Holmberg *et al.*, 1976), and one chronic bioassay exposed animals for 76 weeks (Maltoni and Cotti, 1988). These exposure durations are too short to evaluate carcinogenicity. Feron *et al.* (1981) exposed animals for 135-144 weeks, based on the point at which 75% of the control rats were dead. Two chronic inhalation bioassays tested only a single concentration of vinyl chloride (Holmberg *et al.*, 1976; Maltoni and Cotti, 1988). Therefore, the studies have limited human relevance.
Outcome Assessment	All bioassays observed animals over their entire lifetimes or examined animals until moribund or following spontaneous death, which could have biased results.

Table K.5 Vinyl Chloride and Bladder Cancer Chronic Toxicity Study Quality Assessment

Citation	Strengths	Weaknesses	Human Relevance
Chronic – Ingestion			
Feron *et al.* (1981)	**Reporting** **Allocation Bias** **Chemical Administration and Characterization**	**Sample:** Not all animals were accounted for **Exposure Conditions**: Exposure period too long **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	**Reporting Bias**	**Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for; small sample size in certain bioassays **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short **Outcome Assessment**: Observation period too long	**Limited:** Low study quality
Chronic – Inhalation			
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	**Bias**	**Reporting:** No bladder tumor data **Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for; small sample size in certain bioassays **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long	**None:** No bladder tumor data
Holmberg *et al.* (1976)	**Bias**	**Reporting:** No bladder tumor data **Allocation:** Did not specify whether random **Sample**: Small sample size **Chemical Administration and Characterization:** Did not identify vinyl chloride source or confirm purity **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment**: Observation period too long	**None:** No bladder tumor data
Maltoni and Cotti (1988)	**Chemical Administration and Characterization Bias Sample**	**Reporting:** No bladder tumor data **Allocation:** Did not specify whether random **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment:** Observation period too long	**None:** No bladder tumor data
Chronic – Intraperitoneal Injection			
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	**Bias**	**Reporting**: No bladder tumor data **Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for; small sample size **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment**: Observation period too long	**None:** No bladder tumor data

Attachment L

Curriculum Vitae

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Areas of Expertise

Epidemiology, toxicology, systematic review, evidence integration, meta-analysis, carcinogenesis, dose-response analysis, product safety, risk assessment, risk communication.

Education & Certifications

Ph.D., Environmental Health Sciences/Toxicology, Johns Hopkins Bloomberg School of Public Health, 2002

Sc.M., Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2000

S.B., Environmental Engineering, Massachusetts Institute of Technology, 1996

Diplomate, American Board of Toxicology (DABT), 2005; recertified 2010, 2015, 2020, 2025

Fellow, American College of Epidemiology (FACE), 2014

Fellow, Academy of Toxicological Sciences (ATS), 2014; recertified 2019, 2024

Professional Experience

2004 – Present GRADIENT, Boston, MA
Principal. Evaluate toxicity and epidemiology data in the context of causation analysis and human health risk assessments. Focus on substances in consumer products, pharmaceuticals, and medical devices, and chemicals in the workplace and the environment.

2009 – 2017 HARVARD T. H. CHAN SCHOOL OF PUBLIC HEALTH, Boston, MA
Adjunct Faculty Member. Department of Epidemiology. Co-instructor of course entitled, "Research Synthesis & Meta-analysis."

2002 – 2004 NATIONAL CANCER INSTITUTE, Bethesda, MD
Cancer Prevention Fellow. Conducted a number of molecular epidemiology studies analyzing the relationships between inflammatory gene polymorphisms and colon cancer risk. Instrumental in the development of a powerful statistical tool for cancer risk assessment.

Continuing Education Courses and Other Training

- Introduction to Open-Access Computational Toxicology Tools (web course), Society of Toxicology 2020 Annual Meeting, April 2020
- Protecting Human Research Participants Online Course, National Institutes of Health (NIH) Office of Extramural Research, 2015
- Tools and Technologies in Translational Toxicology, Society of Toxicology 2013 Annual Meeting, San Antonio, TX, March 2013

- Use of Expert Elicitation to Inform Decisionmaking, Society for Risk Analysis 2012 Annual Meeting, San Francisco, CA, December 2012
- Novel Statistical Challenges in Environmental Epidemiology Workshop, 3rd North American Congress of Epidemiology, Montreal, Canada, June 2011
- Comparative Biology of the Lung, Society of Toxicology 2010 Annual Meeting, Salt Lake City, UT, March 2010
- Introduction to the Benchmark Dose Methodology and Interactive Application of United States Environmental Protection Agency (US EPA) Benchmark Dose Software (BMDS), Version 2.1, Society for Risk Analysis 2010 Annual Meeting, Salt Lake City, UT, December 2010
- Green Innovation for Business Conference (Moderator, Green Chemistry and Greenwashing Workshops), Boston, MA, June 2009
- Decision-making for Recommendations and Communication Based on the Totality of Food-related Research, International Life Sciences Institute Workshop, Washington, DC, December 2008
- 2008 Board of Health Certification Program, Massachusetts Association of Health Boards, Marlborough, MA, November 2008
- What is Evolutionary Epidemiology? American College of Epidemiology Annual Meeting, Tucson, AZ, September 2008
- Research Ethics in Studying Genes and the Environment in Diabetes Among Ethnic Minorities, American College of Epidemiology Annual Meeting, Tucson, AZ, September 2008
- Use of Data for Development of Uncertainty Factors in Non-Cancer Risk Assessment, Society of Toxicology 47th Annual Meeting, Seattle, WA, March 2008
- International Society of Regulatory Toxicology and Pharmacology Workshop: Conducting and Assessing the Results of Endocrine Screening, Bethesda, MD, February 2008
- Assessment of Abuse Liability and Physical Dependence, Northeast Chapter Society of Toxicology Annual Meeting, Groton, CT, October 2007
- Practical Issues and Procedures for Preclinical Safety Testing, 2007 BioReliance Toxicology Technical Seminars, Boston, MA, October 2007
- Introduction to Pharmacoepidemiology: Practical Applications and Analytic Methods, American College of Epidemiology 25th Annual Meeting, Ft. Lauderdale, FL, September 2007
- SAS Programming I: Essentials, SAS Institute, Boston, MA, July 2007
- Introduction to Bayesian Modeling of Epidemiologic Data, Society for Epidemiologic Research 40th Annual Meeting, Boston, MA, June 2007
- Systematic Review and Meta-analysis, Society for Epidemiologic Research 40th Annual Meeting, Boston, MA, June 2007
- The Biology and Toxicology of the Peri- and Post-natal Development, Society of Toxicology 46th Annual Meeting, Charlotte, NC, March 2007
- Reproductive Toxicity Testing: Study Designs, Evaluation, Interpretation, and Risk Assessment, Society of Toxicology 45th Annual Meeting, San Diego, CA, March 2006
- Project Managers Bootcamp I, PSMJ Resources, Inc., Cambridge, MA, April 2005
- Development and Interpretation of Toxicokinetic Data for Risk and Safety Assessment, Society of Toxicology 44th Annual Meeting, New Orleans, LA, March 2005
- Survival Analysis, Graduate Summer Institute of Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, June 2003
- Speaking on the Job, Cancer Prevention Fellowship Program, National Cancer Institute (NCI), Rockville, MD, February 2003
- Grants and Grantsmanship Workshop, Cancer Prevention Fellowship Program, NCI, Rockville, MD, January 2003
- Spotted Gene Expression Microarray Workshop, Advanced Technology Center, NCI, Gaithersburg, MD, October 2002
- Laboratory of Cellular Carcinogenesis and Tumor Promotion/Laboratory of Human Carcinogenesis/Laboratory of Experimental Carcinogenesis Interlaboratory Seminar, Monthly, 2002-2004
- Division of Cancer Prevention, Office of Preventive Oncology Colloquia Series on Cancer Prevention Topics, Weekly, 2002-2004

- Radiation Safety for Authorized Users, NIH Radiation Safety Branch, Bethesda, MD, Sept. 2002
- Molecular Prevention Course, NCI Summer Curriculum in Cancer Prevention, Rockville, MD, August 2002
- Principles & Practice of Cancer Prevention and Control Course, NCI Summer Curriculum in Cancer Prevention, Rockville, MD, July-August 2002

Professional Activities

- Member, American College of Epidemiology (ACE) Ethics & Policy Committee, 2024-Present
- Philanthropy Liason, National Charity League, 2023-Present
- Member, Evidence-based Toxicology Collaboration (EBTC) Interim Scientific Advisory Council (iSAC), November 2021-Present
- Member, Board of Directors, Academy of Toxicological Sciences, 2020-2023, 2024-Present
- Chair, Communications Committee, Academy of Toxicological Sciences, 2021-2022
- Member, Communications Committee, Academy of Toxicological Sciences, 2020-2021
- Canton, Massachusetts, COVID Task Force, 2020-Present
- Scientific Advisory Board Member, National Stone, Sand, and Gravel Association, 2019-Present
- Invited Lecturer, "Introduction to Meta-analysis," Northeastern College of Professional Studies, May 8, 2019
- Invited Participant, "Excellence in Risk Analysis," Society for Risk Analysis (SRA) Workshop, June 2018
- Reviewer, R21 Hurricane Applications, National Institutes of Health (NIH), January 2018
- Member, Regis College Doctoral Thesis Committee, 2015-2017
- Reviewer, R21 NIH Exploratory/Developmental Research Grant Proposal, NIH, September 2017
- Invited Panelist, Cancer Prevention Fellowship Program (CPFP) Alumni Career Panel, September 2016
- Reviewer, K99 Career Research Grant Proposal, NIH, July 2016
- Invited Lecturer, "An Introduction to Meta-analysis," Johns Hopkins Bloomberg School of Public Health, April 5, 2016
- Member, Scientific Advisory Council, Evidence-based Toxicology Collaboration (EBTC) at Johns Hopkins Bloomberg School of Public Health, December 2015-November 2021
- Invited Observer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*: *Volume 113: Some Organochlorine Insecticides and Some Chlorophenoxy Herbicides*, Lyon, France, June 2015
- Mentor, Society of Toxicology Mentor Match Program, January 2015-Present
- Member, Speaker Bureau, Society of Toxicology, July 2014-2016
- Chair, "Implementing NRC Recommendations: IRIS," SRA Annual Meeting, 2014
- Member, California Breast Cancer Research Program (CBCRP) Chemicals Testing and Occupational Exposures Review Panel, November 2014
- Proposal Reviewer, Scientific Panel, California Breast Cancer Research Program (CBCRP), June 2014
- Invited Epidemiology Panel Member, The International Council of Chemical Associations Long-Range Research Initiative and Joint Research Centre Workshop, "What is Safe? Integrating Multi-Disciplinary Approaches for Decision Marking about the Human Health and Environmental Impacts of Chemicals." Lugano, Switzerland, June 2014
- Proposal Reviewer, John Templeton Foundation, 2014
- Co-Chair, "Understanding Weight of Evidence: Exploring Different Approaches to Integrating Evidence from Diverse Data Streams," Society of Toxicology, 2014
- Co-Chair, "Epidemiology for Toxicologists: What the Numbers Really Mean," Society of Toxicology, 2014
- Best Paper Awards Selection Committee, Risk Assessment Section, Society of Toxicology, 2014
- Peer Reviewer, Provisional Peer-Reviewed Toxicity Values for Styrene-Acrylonitrile (SAN Trimer), US EPA Draft Document, December 2013
- Keynote Speaker and Scientific Committee Member, Isocyanates & Health Conference, April 2013
- Presidential Task Force Member, Strategic Plan, American College of Epidemiology, 2013

- Proposal Reviewer, National Science Foundation, 2013
- Invited Participant, ILSI Health and Environmental Sciences Institute Emerging Issue Workshop: Evaluating Causality in Epidemiology, October 2012
- Invited Panel Member, "Using Mode of Action to Support the Development of a Multipollutant Science Assessment," US EPA Workshop, May 2012
- Editorial Board Member, *Carcinogenesis*, 2012-2014
- Invited Participant on "Improving Science-Based Regulation," The George Washington University Regulatory Studies Center and the Center for Risk Science and Public Health, January 2012
- Member, Massachusetts Environmental Justice Assistance Network (EJAN), 2010-Present
- Board Member, American College of Epidemiology, 2011-2013
- Nominating Committee, Society of Toxicology, 2009-2011
- Elected Member, Canton, Massachusetts Board of Health, 2008-Present
- Editorial Board Member, *The Open Biomarkers Journal*, 2008-Present
- Managing Editor, *Journal of Environmental Protection Science*, 2008-2010
- Member, Canton, Massachusetts Medical Reserve Corps, 2007-Present
- Peer Reviewer, *Texas Commission on Environmental Quality, Development Support Document for Nickel and Inorganic Nickel Compounds, Preliminary Draft*, May 2009
- Invited Observer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100, Meeting C: Metals, Particles and Fibres*, Lyon, France, March 2009
- Abstract Awards Selection Committee, Risk Assessment Section, Society of Toxicology, 2008
- Secretary/Treasurer, Risk Assessment Specialty Section, Society of Toxicology, 2007-2009
- Editorial Board Member, *Journal of Environmental Protection Science*, 2007-2008
- Guest Lecturer, Cancer Epidemiology, University of Maryland, 2004
- Member, Cancer Prevention Fellowship Scientific Education Committee, NCI, 2003
- Guest Lecturer, Xenobiotic Metabolism, Johns Hopkins Bloomberg School of Public Health, 2001-2002
- Reviewer: *African Journal of Biotechnology; American Journal of Ophthalmology; American Journal of Pathology; Annals of Epidemiology; Applied Economics Letters; Biomarkers & Prevention; BMC Medical Research Methodology; Cancer Epidemiology; Cancer Genetics and Cytogenetics; Cancer Research; Carcinogenesis; Chemical Research in Toxicology; Chemico-Biological Interactions; CHEST; Clinical Cancer Research; Critical Reviews in Toxicology; Environmental Health Perspectives; Environment International; Environmental Science & Technology; Epidemiology; Food Science & Nutrition; Global Epidemiology; Human and Experimental Toxicology; Inhalation Toxicology; International Journal Of Environmental Health Research; International Journal of Environmental Research and Public Health; Journal of Cellular Biochemistry; Journal of Clinical Epidemiology; Jornal de Pediatria; Journal of Exposure Science and Environmental Epidemiology; Journal of Human and Ecological Risk Assessment; Journal of Occupational and Environmental Medicine; Journal of Toxicology and Environmental Health, Part A: Current Issues; Medical Journal of Australia; NeuroToxicology; PeerJ; Pharmacogenetics; Preventive Medicine Reports; Regulatory Toxicology and Pharmacology; Risk Analysis; Safety and Health at Work; Scientific Reports (Nature Publishing Group); Toxicology; Toxicology and Applied Pharmacology; Toxicological Sciences; Trends in Food Science & Technology*

Honors and Awards

- Best Poster Award, Environment, Health & Safety Poster Session, Polyurethanes Technical Conference, October 2018
- Distinguished Alumna Award, Johns Hopkins University, April 2015
- Chauncey Starr Distinguished Young Risk Analyst Award, Society for Risk Analysis, 2014
- Best Overall Abstract, Risk Assessment Specialty Session, Society of Toxicology, San Antonio, TX, 2013
- International Dose-Response Society Outstanding New Investigator Award, 2012
- Top 10% Best Overall Abstracts in Risk Assessment, Risk Assessment Specialty Section, Society of Toxicology, Seattle, WA, 2008

- Fellows Award for Research Excellence: $1,000 Travel Award, National Institutes of Health, Bethesda, MD, 2004
- Honorable Mention Poster Presentation, Center for Cancer Research 4th Annual Fellows and Young Investigators Retreat, Williamsburg, VA, March 2004
- Graduate Student Travel Award, Gordon Research Conference on Hormonal Carcinogenesis, 1999, 2001
- Travel Award, Third World Congress on Alternatives and Animal Use in the Life Sciences, Bologna, Italy, 1999
- Howard Hughes Predoctoral Fellowship Award, 1997-2002
- NIEHS Training Grant Graduate Fellowship Award, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 1996-1997
- Tau Beta Pi, National Engineering Honor Society, 1995-1996
- Chi Epsilon, National Civil Engineering Honor Society, 1994-1996

Professional Affiliations

American College of Epidemiology; Society for Risk Analysis; Society for Risk Analysis New England Chapter; Society of Toxicology; American Board of Toxicology; Academy of Toxicological Sciences; International Dose-Response Society

Selected Projects

Manufacturer: Evaluated whether potential exposures to ammonium perfluorooctanoate (APFO) and perfluorooctanoic acid (PFOA) emissions from a manufacturing facility could have caused specific cancer and non-cancer health outcomes in certain individuals.

Manufacturer: Evaluated whether certain cancers could have been caused by exposure to an alleged NDMA impurity in a pharmaceutical.

Trade Association: Conducted a systematic review of gas cooking or indoor nitrogen dioxide (NO_2) and asthma or wheeze in children.

Food company: Reviewed applicable US FDA requirements for new dietary ingredients and proposed a framework where alternative test data could be used to reduce or replace traditional animal toxicity testing.

Trade Organization: Created a database and conducted hazard assessments for approximately 800 chemicals.

Town: Reviewed a cancer cluster analysis conducted by the state and communicated findings to the community.

University: Described the main features of internal dose time courses that are important when pharmacodynamics are governed by an activation threshold. Presented the adverse outcome pathway (AOP) for NLRP3-induced chronic inflammatory diseases as a case study.

Trade Organization: Evaluated the Consumer Product Safety Commission's Final Rule: Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates, including the methods used to calculate Hazard Index values.

Cleaning Products Company: Determined whether several ingredients of several cleaning products could have caused or exacerbated several claimed health effects (such as respiratory effects) in individuals using the products or working in areas where the products were used.

Public School: Evaluated school facility information and environmental assessments that have been conducted on lead in school drinking water. Quantified typical student exposures and estimated health risks. Evaluated exposures and risks of PEX replacement pipes.

Research Organization: Estimated dietary phthalate intake based on data from the National Health and Nutrition Examination Survey (NHANES), a program of studies of United States residents conducted at the Centers for Disease Control and Prevention (CDC).

Trade Association: Reviewed and provided comments to the United States Environmental Protection Agency (US EPA) on its assessment plan for an updated arsenic health risk assessment.

Trade Organization: Developed a framework for a systematic, objective, and transparent evaluation of the evidence for non-cancer causation that requires reviewers to conduct a systematic study quality analysis and consider how the evidence from several realms impacts the interpretation of others.

Electric Utility: Evaluated the potential non-cancer and cancer health effects from exposure to coal combustion residuals (CCR) as a whole, and arsenic and chromium specifically, as reported in epidemiology and toxicity studies. Determined whether potential exposures to CCR contributed to current or future health effects, or warrant medical monitoring.

Trade Organization: Determined the safety of benzoic acid and its salts when used as preservatives in food and soft drinks based on an evaluation of pharmacokinetic data in rodents and humans, and human clinical studies of sodium benzoate administered as a therapeutic drug.

Children's Personal Care Product Manufacturer: Conducted a comprehensive hazard and risk assessment using data reported by various research and regulatory agencies, and specific risk assessments for individual preservatives, to determine whether there could be health risks for children from regular use of personal care products containing these preservatives.

Trade Organization: Evaluated the association between coffee generally, and acrylamide specifically, and cancer risk in the context of California's Proposition 65.

Trade Association: Conducted two comprehensive critical weight-of-evidence (WoE) reviews of studies bearing on the ability of very low bisphenol a (BPA) exposures to affect reproduction and development *via* endocrine disruption. These analyses were presented to several state legislative committees, all of which were considering bans on BPA.

Trade Organization: Conducted a survey of nearly 50 WoE frameworks to evaluate best practices for determining causation. Defined the key concepts of WoE analyses and their application to particular problems, and articulated the best practices from among the spectrum of approaches.

Food Manufacturer: Evaluated the significance of lead in imported hot sauces after a journal article reported that some of the products contained elevated levels of lead. Prepared a critique and summary of the study findings, and compared lead levels to US FDA limits. Evaluated the potential impact of the lead exposures on blood lead levels.

Trade Organization: Evaluated potential health risks from BPA in epoxy-lined metal cans based on both peer-reviewed scientific literature and regulatory agency risk assessments.

Personal Care Product Company: Conducted a risk assessment of zinc oxide in sunblock.

Trade Association: Critically evaluated the Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP-CE) that US EPA uses in the risk assessments for ozone (O_3) and particulate matter (PM) as part of its NAAQS evaluation.

Chemical Company: Evaluated the utility of using epidemiology data in human health risk assessment and regulatory decision-making for the insecticide, chlorpyrifos.

Trade Organization: Performed an O_3 mortality risk assessment using US EPA's Environmental Benefits Mapping and Analysis Program (BenMAP). Evaluated mortality risks by conducting a series of sensitivity analyses to assess how alterative model inputs impacted risk results.

Hospitals: Conducted screening level risk assessment for contaminants, including hexavalent chromium and polycyclic aromatic hydrocarbons, in product residue on surgical instruments used for medical procedures at several hospitals.

Industrial Consortium: Contributed to a toxicity and risk assessment in a class-action lawsuit by residents claiming adverse health effects from TCE and PCE in groundwater. Participated in a quantitative analysis of ingestion exposure, showering exposure, potential health risks, and proposed medical monitoring.

Water Supply Company: Evaluated potential health effects of arsenic, lead, and chlorination disinfection byproducts in drinking water.

City: Evaluated whether a career as a firefighter is associated with brain or lung cancer.

Consumer Product Company: Reviewed the safety testing required for a pesticide to be registered in the US; the potential risks and benefits of DEET; and standards, guidelines, and recommendations for using DEET.

Law firm: Evaluated whether air pollution may have increased the incidence and prevalence of several health conditions, including several cancers, in a city in Israel.

Trade Organization: Evaluated whether there is a scientific consensus regarding the potential health effects of asbestos compared to other elongate mineral particles, and whether any differences should be considered for testing guidelines.

Consumer Product Company: Critically reviewed epidemiology studies of specific consumer products.

Mining Company: Assessed the potential health risks of residents exposed to nickel as result of residing near a surface lateritic nickel mine and ferronickel smelter based on air, water, soil, and sediment data collected as part of the mine's environmental monitoring program.

Trade Association: Conducted a systematic review ozone exposure and metabolic syndrome.

Trade Organization: Critically reviewed parabens and weight gain epidemiology, toxicology, and mode-of-action evidence.

Waste Disposal Company: Evaluated the scientific evidence regarding radiation exposure and renal cell carcinoma in general and the likelihood that this cancer could have been caused by exposure to radionuclides from living in proximity to a landfill containing radioactive waste.

Trade Organization: Reviewed a cancer cluster investigation and epidemiology studies of pediatric leukemia and lymphoma, pediatric brain cancer, and pediatric Ewing sarcoma.

Trade Organization: Critically reviewed epidemiology research on air pollution and COVID.

Trade Organization: Evaluated and provided comments on US EPA's draft risk evaluation for trichloroethylene. Focused on the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin's lymphoma.

Non-Profit Research Institute: Developed an *in silico*-based health-protective screening approach for inhaled chemicals.

Law firm: Evaluated the potential human carcinogenicity of formaldehyde and methyl *tert*-butyl ether (MTBE).

Trade Organization: Conducted a systematic review of long-term exposure to fine particulate matter ($PM_{2.5}$) and all-cause mortality.

Waste Management Company: Evaluated whether specific health conditions, including cancer, were likely attributable to exposures to Radium 226, Thorium 230, or Uranium 238 that originated from a landfill.

Farm: Evaluated whether certain health conditions could be caused by exposures to nitrate in drinking water or hydrogen sulfide or ammonia in air and, if so, under what exposure conditions.

Trade Organization: Conducted a WoE analysis of talc and ovarian cancer, including a quantitative bias analysis of epidemiology studies.

Trade Organization: Evaluated the association between personal $PM_{2.5}$ exposures and ambient $PM_{2.5}$ concentrations, and the implications for the interpretation of epidemiology studies that estimate personal exposure based on ambient concentrations.

Private Company: Assessed whether appropriate epidemiology methods were used to evaluate a potential pediatric cancer cluster in a military housing complex. Evaluated whether public health and environmental investigations used methodologically sound analyses.

Consumer Product Company: Determined whether a framework for assessing the hazard of cleaning product ingredients was sufficient to support "non-toxic" claims on product packaging for a household cleaner.

Consumer Product Company: Evaluated the historical state of knowledge regarding the toxicity of butadiene and the development of myelodysplastic syndrome.

Railroad Company: Summarized the historical states of knowledge regarding the toxicity of vermiculite and asbestos in the railroad industry.

Trade Organization: Conducted a systematic review of metallic nickel and cancer.

Trade Organization: Evaluated best practices for evidence integration in National Ambient Air Quality Standards (NAAQS) Integrated Science Assessments (ISAs).

State Environmental Agency: Quantitatively evaluated how uncertainty and bias can impact epidemiology associations between air pollutants and respiratory morbidity at low exposures.

Law Firm: Evaluated the potential lung cancer, mesothelioma, and interstitial fibrosis risks from exposure to chrysotile asbestos from brakes based on epidemiology studies of vehicle brake repair workers and industrial hygiene, mode-of-action, and toxicology data.

Chemical Company: Evaluated and provided comments on US EPA's Toxicological Review of Libby Amphibole Asbestos. Interacted with several regulatory agencies throughout the interagency process of the Integrated Risk Information System (IRIS) review.

Trade Organization: Evaluated systematic review methods used by US EPA in IRIS and Toxic Substances Control Act (TSCA) evaluations.

Pesticide Companies: Evaluated the use of neurodevelopmental epidemiology studies by the US EPA in the re-registration process for organophosphate pesticides.

Consumer Product Company: Determined whether aspiration of a laundry pod caused long-term health effects in an infant.

Consumer Product Company: Evaluated the implications of a new toxicity study of an ingredient in a consumer product for adults and children who use the product and workers who manufacture the product. Provided an analysis of the potential Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Safety Data Sheet (SDS) implications of a the ingredient.

Trade Organization: Assessed whether a post-market skin patch epidemiology study should be used for risk assessment.

Trade Organization: Evaluated emission limits for several chemicals defined in certification guidelines for a consumer product.

Trade Organization: Reviewed and provided comments on Health Canada's Draft Screening Assessment Report and Risk Management Scope for talc.

Municipality: Evaluated whether childhood blood lead levels in a city appeared to be impacted by increases in water lead levels. Assessed the potential beneficial impact of the City's distribution of point-of-use water filters to residents.

Trade Organization: Developed detailed criteria for exposure characterization that can be used when designing future epidemiology studies and for evaluating completed studies to determine how their results should be considered in a regulatory setting.

Trade Organization: Determined whether nickel should be classified as a reproductive or developmental toxicant under California EPA's Proposition 65.

Consumer Product Company: Developed a statistical approach for a clinical study of a medical device.

Trade Organization: Performed a detailed quantitative analysis to determine the reliability and adequacy of the T25 Carcinogenic Potency Method for inhalation exposures of inorganic substances. This method is used to classify carcinogenic substances according to the European Union's guidance for Classification, Labelling and Packaging of Substances and Mixtures.

Law Firm: Evaluated the potential side effects and dose-response relationships for cosmetic botulinum toxin injections from reviews of clinical trials and FDA warning labels. Assessed whether claimed health effects in an individual existed prior to an injection with botulinum toxin, were included among the documented side effects of the toxin, or were indicative of systemic toxicity.

Trade Organization: Critically reviewed the draft recommendation for a non-health-based BPA occupational exposure limit (OEL) proposed by the Dutch Expert Committee on Occupational Health and Safety (DECOS). Derived and recommended a health-based BPA OEL that is consistent with European Commission directives.

Law Firm: Evaluated nickel concentrations in an urban neighborhood using air monitoring data. Assessed the cancer and non-cancer health risks of exposure to nickel in air and dust among residents.

Trade Organization: Evaluated the association between short-term exposures to $PM_{2.5}$ and hospital admissions for cardiovascular diseases.

Research Organization: Evaluated the impact of respiratory infections, outdoor pollen, and socioeconomic status on associations between $PM_{2.5}$ and ozone and pediatric asthma hospital admissions.

Research Organization: Critically reviewed the epidemiology literature on exposure to $PM_{2.5}$ and several birth outcomes.

Trade Organization: Reviewed and commented on the International Agency for Research on Cancer (IARC) Preamble, which summarizes the underlying scientific principles of the IARC Monographs, which evaluate the carcinogenic hazards of chemicals and other substances.

Baby Product Company: Evaluated whether a teething ring product contained more Bisphenol A than is permitted under Proposition 65.

Energy Company: Evaluated whether working on the site of a former Manufactured Gas Plant may have contributed to kidney cancer.

Steel Company: Assessed the state of knowledge related to employment in a steel mill or steel plant and asbestos-related disease to understand when the scientific community began to study the hazards of asbestos among steelworkers and when it was reasonable for a steel manufacturing company to have known that exposure to asbestos-containing materials could potentially lead to the development of respiratory disease in steelworkers.

Trade Organization: Evaluated US EPA's calculation of an inhalation unit risk (IUR) in its "Toxicological Review for Trichloroethylene in Support of Summary Information on the IRIS."

Trade Organization: Developed standards for epidemiology studies similar to good laboratory practice (GLP) standards, which are intended to assure the quality and integrity of non-clinical laboratory studies.

Manufacturer: Critically reviewed the quality of case-control studies conducted in North America that assessed the associations between captan exposure and the risk of multiple myeloma. Conducted a quantitative bias/uncertainty analysis of these studies.

Trade Organization: Evaluated the basis for the American Conference of Governmental Industrial Hygienists (ACGIH) lowering the Threshold Limit Value for toluene diisocyanate.

Law Firm: Evaluated exposure to O-toluidine and bladder cancer risk.

Law Firm: Evaluated exposures to landfill gases, including hydrogen sulfide, and potential health effects from these exposures in individuals residing near a municipal solid waste landfill. Evaluated potential odor impacts and the differences between odor perception and adverse health effects.

Trade Organization: Reviewed literature regarding several air toxics and health endpoints and provided recommendations on a proposed regulation in California to monitor communities for air pollution-attributable health effects.

Trade Organization: Critically reviewed the harmonized carcinogenicity classification and labeling for cobalt metal developed to comply with the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation by RIVM (Netherlands National Institute for Public Health and the Environment).

Toy Manufacturer: Evaluated whether brain injury could occur as a primary consequence of ingesting toy beads containing 1,4-butadiene, or as a secondary consequence of experiencing coma-like symptoms following ingestion of the beads.

Pharmaceutical Company: Assessed whether on-label use of a pharmaceutical increased cardiovascular disease risk based on randomized controlled trials and observational epidemiology studies.

US EPA: Contributed to the design of a model describing several frequently encountered toxicity endpoints in terms of a series of progressive pathophysiological steps.

Pharmaceutical Company: Performed an in-depth analysis of the toxicology and epidemiology data of a specific drug to determine whether the company could have anticipated potential adverse side effects in humans.

Pharmaceutical Company: In the context of a patent infringement lawsuit, performed an independent analysis of efficacy and toxicity data from animal experiments to determine if claims in the patent could be challenged.

Government Agency: Critically evaluated an epidemiology study of exposures and health outcomes in indigenous and Afro-Colombian communities living near a nickel mine and smelter and discussed with the government agency that conducted the study.

Chemical Company: Conducted a meta-analysis of epidemiology studies that evaluated the use of a pharmaceutical during labor and dystocia.

Trade Association: Evaluated whether atherosclerosis development is a plausible mode of action for PM in cardiovascular pathogenesis, and whether this is supported by epidemiology evidence.

Trade Association: Critically reviewed the draft recommendation for a non-health-based OEL for di- and triisocyanates proposed by the DECOS of the Health Council of the Netherlands.

Trade Organization: Developed a database of epidemiology studies of occupational exposures to pesticides and cancer.

Trade Organization: Critically reviewed the epidemiology literature on long-term exposure to ambient ozone and asthma development.

Manufacturer: Evaluated the health risks of potential carbon monoxide exposures at a proposed bridge near a manufacturing facility.

Consumer Product Company: Systematically reviewed epidemiology, toxicity, exposure and transport, and mechanistic studies to evaluate whether personal use of cosmetic talc increases ovarian cancer risk.

Trade Organization: Evaluated whether an alternative form of the sulfur dioxide (SO_2) NAAQS would be as public health protective as the then-current form.

Trade Organization: Critically reviewed the approach US EPA used to quantify health co-benefits when assessing the impacts of the Clean Power Plan. Evaluated the scientific validity of the models, data sources, and assumptions underlying US EPA's calculations.

Chemical Company: Evaluated whether exposure to odorous chemicals emitted from spray foam insulation in a residence posed a potential health risk. Compared residents' exposure to odor thresholds, toxicity criteria, and health effect levels for specific constituents emitted from the foam.

Law Firm: Assessed human health risks associated with coal-fired power plant emissions, including particulate matter, SO_2, and nitrogen oxides (NO_x), based on air modeling results and available measurement data.

Trade Organization: Conducted a systematic review of epidemiology studies that evaluated proximity to unconventional natural gas development (UNGD) and perinatal outcomes.

Chemical Company: Provided chemical-level assessments (*i.e.*, analysis of inventory status, occupational exposure limits, and available toxicity data) and product-level assessments (*i.e.*, evaluation of Good Manufacturing Practice and regulatory hurdles) for several cosmetics and consumer products.

Research Organization: Critically evaluated toxicity studies that investigated $PM_{2.5}$ and developmental and reproductive effects.

Utility Group: Evaluated potential exposures and health impacts of PM in general, as well as two specific types of PM associated with power plant operations (*i.e.*, diesel exhaust emissions and coal dust emissions).

Manufacturer: Assessed the potential health risks of saline-filled breast implants based on a review of the peer-reviewed literature and pre- and post-market studies of silicone- and saline-filled breast implants.

Pharmaceutical Company: Evaluated whether historical data support the patentability of a drug that lowers blood lipid levels. Reviewed the experimental methods (including statistics) and results of efficacy studies with the drug to confirm the original study conclusions.

Trade Associations: Facilitated research that addresses the causality of the relationship between $PM_{2.5}$ and mortality. Selected research candidates, developed a request for proposal, evaluated solicited proposals, coordinated selected researchers for data access, and organized a symposium for researchers to present and discuss their findings.

Utility Company: Evaluated health effects associated with potential exposures to chemicals, including coal tar and polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene, resulting from recreational activities in the vicinity of a former manufactured gas plant site.

Chemical Company: Evaluated whether the PAHs in an asphalt roofing underlayment would require its classification under the Occupational Safety and Hazard Administration's (OSHA) hazard communication standard.

Manufacturer: Evaluated the incidence, prevalence, risk factors, and potential alternative causes of health complaints among office workers allegedly exposed to chemicals in indoor air *via* vapor intrusion of contaminated groundwater. Also assessed whether there were any disease clusters at the site.

Trade Organization: Provided written and oral comments to the Clean Air Scientific Advisory Committee (CASAC) on exposure, epidemiology, toxicity, and mode-of-action studies and their bearing on US EPA's development of NAAQS for O_3, PM, NO_x, and sulfur oxides (SO_x) on numerous occasions.

Manufacturer: Reviewed asbestos exposure data related to the handling and installation of electrical equipment and epidemiology evidence regarding mesothelioma, lung cancer, and laryngeal cancer in electricians.

US Army: Assessed several dose-response functions, animal models, and endpoints to obtain the most appropriate model-predicted risk estimate to use in establishing a risk-based inhalation exposure criterion for vanadium pentoxide.

Appliance Manufacturer: Evaluated evidence for a cancer cluster in a neighborhood where soil containing polychlorinated biphenyl (PCBs) was historically used as landfill in a recreation area.

State Environmental Agency: Conducted WoE evaluations of the association between short-term and long-term ozone exposure and cardiovascular effects.

State Environmental Agency: Evaluated how meta-analyses have been or could be applied in the evaluation of health effects of air pollutants. Assessed the strengths and limitations of methods, issues that arise in meta-analyzing different types of data, assumptions that can influence the interpretation of results, and how bias and heterogeneity can be addressed.

Law Firm: Assessed the impact of coal-fired power plant emissions on exposures to fine PM, SO_2, and NO_2 and whether these exposures likely contribute to adverse health effects in Colorado residents.

Mining Company: Evaluated methods used to derive a proposed standard for nickel by the Province of Quebec, Canada.

Utility Company: Reviewed the historical releases of compounds associated with manufactured gas plant processes, including PAHs such as benzo[a]pyrene, and the historical understanding of risk assessment, carcinogenesis, and the toxicity of these compounds.

State Environmental Agency: Reviewed epidemiology, controlled human exposure, experimental animal, and mechanistic studies of ozone and markers of inflammation and oxidative stress.

State Environmental Agency: Critically reviewed potential uses of Next Generation (NexGen) toxicity testing methods and associated interpretation techniques in assessing the risks associated with chemical exposures (*e.g.*, in high-throughput screening programs or detailed quantitative analyses for individual data-rich chemicals).

Trade Organization: Critiqued draft templates for tabulating epidemiology and experimental animal study data for hazard identification proposed by the Developmental and Reproductive Toxicant Identification Committee (DART IC) of California's Office of Environmental Health Hazard Assessment (CalOEHHA). Proposed an alternative set of tables to systematically present data for consideration in a full evidence integration process.

State Environmental Agency: Critically reviewed epidemiology, controlled human exposure, experimental animal, and mechanistic studies of ozone and outcomes related to asthma exacerbation.

State Environmental Agency: Evaluated the relationship between ozone concentrations and asthma hospitalizations in Texas from 2001-2011.

Trade Organization: Conducted sensitivity analyses to determine how alternative assumptions impact exposure and risk estimates calculated using the US EPA Air Pollutants Exposure (APEX) Model.

Health Care Company: Analyzed the health effects of perchloroethylene and its breakdown products (trichloroethylene, 1,1-dichloroethylene, 1,2-dichloroethylene, and vinyl chloride) to address community concerns with remediation requirements. Also reviewed the bases for soil and groundwater remediation goals.

Chemical Company: Analyzed health risks from exposure to PCBs in caulking in a school in Massachusetts by analyzing potential exposures at the school and epidemiology and toxicology evidence. Also summarized the state of knowledge regarding PCBs when the school was built.

State Environmental Agency: Organized and participated in a workshop focused on the scientific evidence for ozone effects and the societal implications of lowering the ozone NAAQS.

Utility Company: Characterized and communicated exposures to chemicals, including PAHs such as benzo[a]pyrene, for occupants of residential and commercial properties constructed on the site of a former manufactured gas plant.

Trade Association: Evaluated non-cancer effects of PM.

Chemical Company: Evaluated whether inflammation and oxidative stress caused by ozone exposure are key events leading to respiratory toxicity.

Chemical Company: Conducted a WoE evaluation of PM and biomarkers of cancer.

Chemical Company: Evaluated whether there was evidence of any developmental health effects clusters at an office building. Assessed likely explanations for health claims.

Trade Association: Proposed a framework for evaluating causation that provides a structure for integrating different realms of evidence, weighing the strength of evidence for causation, and assessing the potential impact of uncertainty on the body of evidence.

Trade Organization: Critically reviewed the epidemiology literature evaluating nickel exposure and reproductive and developmental effects. Determined whether it supported a prioritization of nickel for CalOEHHA's consideration under California's Proposition 65.

Trade Organization: Evaluated whether higher regulatory limits on heavy metals in finished medical marijuana products would provide an adequate margin of safety for patients, and whether certain hydrocarbon gases could be safely used in the production of cannabis concentrates used in medical marijuana infused products.

Law Firm: Evaluated whether exposures to diesel exhaust and jet fuel are associated with lung cancer based on a literature review, agency classifications, and key epidemiology studies on which classifications are based.

Electric Utility: Evaluated the scientific basis of health impacts associated with air quality regulations that would impact an electricity generation facility. Compared air quality data in the area around the facility to health-based NAAQS.

Trade Organization: Assessed the US EPA "Framework for Human Health Risk Assessment to Inform Decision Making" and compared it to US EPA's ongoing O_3 analysis. Focused on planning and "fit for purpose," WoE, transparency, reasonableness, consistency, at-risk factors, and uncertainty and variability.

Electric Utility: Analyzed air monitoring data to determine the potential public health impacts of stack air emissions of fine PM, O_3, NO_2, and SO_2.

Trade Organization: Conducted a quantitative analysis of controlled human exposure studies to address whether there is a subset of individuals who are susceptible to health effects of criteria air pollutants at particular exposure levels, but whose response is obscured by analyzing data at the group level.

Law Firm: Analyzed human health risks posed by chemicals measured in workplace indoor air that were alleged to have originated from groundwater contaminated by a nearby recycling facility. Focused on the epidemiology of the chemicals of concern at the levels measured in the workplace and the plaintiffs' health complaints, including cancer.

Smelter: Assessed whether a smelter's permit would likely allow for SO_2 emissions that could lead to adverse health effects in the community.

Trade Organization: Reviewed the basis for the California Environmental Protection Agency's (CalEPA's) proposal to list SO_2 as a Proposition 65 developmental and reproductive toxicant. Evaluated whether the underlying studies provided sufficient and robust evidence that SO_2 causes developmental and reproductive effects.

Trade Organization: Reviewed and critiqued the assumptions and uncertainties associated with the statistical models on which US EPA's 2011 Benefits and Costs of the Clean Air Act Report was based.

Chemical Company: Evaluated US EPA's proposed national emission standards for hazardous air pollutants (NESHAPs) for mercury from major industrial boilers. Evaluated the agency's statistical approach for establishing the maximum achievable control technology (MACT) limit and determined how alternative approaches would impact the MACT derivation.

Trade Organization: Conducted meta-analyses and meta-regressions of airway hyper-responsiveness in asthmatic volunteers exposed to NO_2 in clinical studies. Presented these analyses to the US Office of Management and Budget.

Trade Organization: Assessed what constitutes an adverse health effect *vs*. normal biological variation (or adaption or compensation to stressors), and the role of statistics in assessing adversity. Used airway hyper-responsiveness to SO_2 as a case study.

Health Effects Institute: Compiled and reviewed studies regarding chronic and acute toxicity guidelines for mobile source air toxicants.

Trade Organization: Evaluated studies examining low-dose exposure to BPA and effects on reproduction and development using a W approach. Discussed results in written comments and oral testimony to CalEPA in the context of whether BPA should be listed as a female reproductive toxicant under Proposition 65.

Cleaning Product Company: Evaluated toxicity of chemicals in all-natural cleaning products.

Municipality: In response to citizens' concerns, independently investigated whether there was an increased incidence of cancer in residents living near a municipal landfill. Communicated findings with city officials and residents at public meetings.

Toy Distributor: Determined whether a toxicological evaluation of a toy was sufficient for determining children's health risks. Assessed the toxicity of a chemical found in the toy, potential routes of exposure, and possible health risks.

Trade Organization: Conducted a systematic review and meta-analyses of 2,4-dichlorophenoxyacetic acid (2,4-D) and non-Hodgkin's lymphoma, gastric cancer, and prostate cancer. Participated as an observer at the IARC Monograph 113 Meeting at which 2,4-D was evaluated.

Trade Organization: Assessed whether animal, mechanistic, and epidemiology evidence is consistent with the nickel ion bioavailability model, which asserts that the carcinogenicity of nickel-containing substances is based on the bioavailability of the nickel ion at nuclear sites of target respiratory epithelial cells.

Public Agency: Evaluated the variability in water lead levels across a US city and the association between water lead levels and blood lead levels in children.

Pesticide Company: Assessed whether epidemiology, toxicology, and mechanistic evidence support chlorpyrifos being a neurobehavioral toxicant in humans at relatively low exposure levels. Evaluated evidence using recently proposed frameworks for integrating human and animal data, as well as Gradient's hypothesis-based weight-of-evidence (HBWoE) approach.

Cleaning Product Company: Evaluated the potential risks of birth defects from exposure to the chemical components of products used in floor stripping and refinishing.

Trade Organization: Conducted a critical examination of a proposal by the National Academy of Sciences that linear low-dose extrapolation should be used for non-cancer and cancer endpoints as a default because measurement error in epidemiology studies linearizes dose-response curves.

Law Firm: Reviewed specific exposure information and occupational epidemiology literature for a claim regarding a causal association between formaldehyde inhalation and acute myeloid leukemia.

Law Firm: Evaluated whether radiation should have been considered as a potential cause of an individual's mesothelioma. Analyzed both specific exposure information and toxicology and epidemiology literature on radiation and mesothelioma.

Trade Association: Using the HBWoE approach, evaluated whether epidemiology, toxicology, and mechanistic evidence supports the plausibility of formaldehyde as a human leukemogen.

Chemical Companies: Calculated a benchmark dose (BMD) for an industrial chemical using US EPA's BMD Software (BMDS). Assessed several dose-response models and evaluated the impact of using historical control data.

Trade Organization: Evaluated whether epidemiology, animal toxicity, mechanistic, and pharmacokinetic evidence indicates that toluene diisocyanate is a human carcinogen.

Trade Organization: Critically reviewed meta-analysis of respiratory cancer risk following inhalation exposure to nickel compounds. Provided comments regarding the methods, limitations, and interpretation of results throughout the conduct of this study.

Trade Organization: Conducted a pilot meta-analysis of studies bearing on the ability of very low oral exposures to BPA to affect prostate weight in rodents. Investigated the possibility of publication bias and evidence for a temporal trend in the data.

Trade Organization: Critically reviewed a draft European Union report on the state of the science regarding endocrine-disrupting chemicals. Assembled a panel of experts to determine whether the draft report constituted a complete and unbiased analysis of endocrine disruptors.

Trade Organization: Reviewed epidemiology studies assessing associations between BPA and several health effects.

Trade Association: Reviewed and prepared comments on ACGIH's proposed Threshold Limit Value for manganese. Reviewed the methodology applied by ACGIH, compared the use of published regression analyses of manganese dose-response data to benchmark dose modeling of more recent data, and identified appropriate adverse effect levels of manganese in occupational studies.

Chemical Manufacturer: Reviewed the epidemiology and mode-of-action data on acetic anhydride and cancer using a systematic WoE approach to determine whether the data are consistent with ACGIH cancer classification.

Law Firm: Evaluated epidemiology literature regarding present and future risks of cancer and non-cancer health effects in a group of individuals from inhalation exposures to trichloroethylene (TCE) and perchloroethylene (PCE).

Law Firm: Evaluated the epidemiology literature regarding cancer and non-cancer health effects of benzene, dioxin, and pentachlorophenol. Conducted a cluster analysis to determine whether individuals residing in an area with alleged exposures had increased rates of several cancers and non-cancer health effects.

Pesticide Companies: Critically reviewed epidemiology, toxicology, and mechanistic studies to assess whether exposure to atrazine in drinking water is associated with reproductive and developmental health effects.

Confidential Client: Evaluated the health effects associated with hexavalent chromium based on an assessment of the epidemiology literature. Assessed the scientific rigor of an analysis of potentially exposed individuals' survey responses.

Trade Organization: Classified, summarized, and entered relevant lead studies into the International Uniform Chemical Information Database (IUCLID) 5.2, a database for the intrinsic and hazard properties of chemical substances that companies can use to submit data under the REACH legislation in Europe.

Trade Organization: Provided written and oral testimony to the US National Toxicology Program (NTP) and its Board of Scientific Councilors regarding occupational epidemiology studies of styrene and whether styrene should be considered a human carcinogen.

Trade Organization: Developed scientifically sound approaches for incorporating human data into quantitative non-cancer risk assessment to support commentary on the ongoing US EPA revision of its dioxin assessment.

Trade Organization: Evaluated the associations between metal exposures and health outcomes using NHANES data.

Trade Organization: Conducted a WoE assessment of exposure to soluble nickel compounds and respiratory cancer risk based on animal carcinogenicity, mode-of-action, and occupational epidemiology studies.

Trade Organization: Conducted a critical review of the US EPA Toxicological Review of 1,4-Dioxane in support of "Summary Information" provided in IRIS. Proposed alternative methods to calculate the cancer slope factor and reference dose.

Law Firm: Evaluated the toxicology and epidemiology evidence regarding several pesticides and whether there was evidence for a causal association with certain birth defects.

Law Firm: Assessed recent occupational epidemiology studies of manganese and their bearing on the reference concentration (RfC).

Law Firm: Assessed whether epidemiology literature supports an association between low-level exposures to lead and IQ.

Trade Organization: Determined whether linear low-dose extrapolation should be used for non-cancer endpoints.

Law Firm: Assessed appropriateness of statistical analyses used by the Ramazzini Foundation for comparing cancer incidence rates in rats treated with MTBE and untreated rats.

Law Firm: Critically reviewed epidemiology literature of radium and osteosarcoma risk. Determined whether osteosarcoma rates were higher than expected in certain geographic regions in a southern state.

Law Firm: Critically reviewed potential health effects associated with exposure to heating oil from a basement spill.

Law Firm: Critically reviewed the epidemiology literature on the role of ionizing radiation in cancer risk in patients receiving radiation therapy, in nuclear energy facility workers, and in patients receiving Thorotrast treatments.

Chemical Company: Conducted a comprehensive review of the scientific literature on indoor dust levels of several flame retardants and an exposure assessment of each one.

Consumer Product Company: Interpreted the results of two genotoxicity screening assays in light of their sensitivity and specificity.

Toy Manufacturer: Conducted failure analyses of children's toys to determine whether proper or improper use was likely to lead to physical harm. Made recommendations regarding ways to make the toys safer.

Chemical Manufacturing Plant: Evaluated the mercury toxicology and epidemiology literature and determined whether levels in residential soil were above background and likely attributable to a nearby manufacturing plant.

Chemical Company: Conducted a critical review of neurodevelopmental toxicity studies of the flame retardant, decabromodiphenyl ether.

Petroleum Refining Company: Conducted an uncertainty analysis of the carcinogenicity of naphthalene using an HBWoE approach.

Power Plant: Critically reviewed published epidemiology studies of health effects in children residing near coal-fired power plants or coal mines. These studies examined respiratory outcomes, birth defects, and effects on physical development.

Law Firm: Analyzed health effects – including fetal, infant, and total death rates and cancer rates – and certain vital statistics in a Montana county. Compared overall health status of the county to that of the state.

Trade Organization: Evaluated and applied an uncertainty analysis focused on dioxin exposure and health effects data from key toxicology and human biomonitoring-based epidemiology studies as part of a margin-of-exposure analysis.

Law Firm: Evaluated toxicology and epidemiology evidence regarding glutaraldehyde and hydroquinone exposure and leukemia.

Trade Organization: Developed and refined a search strategy for the exposure and health effects of a chemical used in a manufacturing process using several databases, such as PubMed, Toxline, IRIS, and HSDB. Identified and screened relevant articles for inclusion in an electronic database.

Cleaning Product Company: Designed methodology for testing the presence and activity of an enzyme in a cleaning product. Determined whether this enzyme was appropriate for the product.

Wood Treatment Plant: Analyzed dioxin and PCB congeners in individuals residing near a wood treatment plant and compared them to background levels reported by NHANES. Analyzed these compounds in soil, dust, and sediment to determine whether there were elevated risks of exposure.

Small Business: Assessed whether cancer cases at a small business could be attributed to a common exposure.

Trade Association: Re-analyzed published rat testicular carcinogenicity data on MTBE using the Poly-3 statistical method to account for survival differences among treatment groups.

Pesticide Company: Analyzed US EPA's use of the lower confidence limit on the benchmark dose ($BMDL_{10}$) to determine a point of departure for the cancer risk of dimethylarsenic acid in humans.

Research Organization: Critically reviewed epidemiology literature to determine if the effects of lead and mercury on human neurological development are additive or synergistic.

Flame Retardant Company: Provided toxicological, database, and risk analysis support for product development of phosphorus-based flame retardant chemicals with low potential for health and environmental impact.

Chemical Company: Contributed to the drafting of an evidence-based argument submitted to US EPA regarding whether acetonitrile should be delisted from the US EPA's Toxic Release Inventory.

Smelter: Reviewed general and company-specific historical knowledge of human and ecological toxicity of smelter contaminants.

Manufacturer: Summarized the cancer and non-cancer effects of cobalt and nickel for a company that fabricates tungsten heavy metal alloy products.

Publications – *Journal Articles*

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Prueitt, RL; Lynch, HN; Zu, K; Shi, L; Goodman, JE. 2018. "Evaluation of Respiratory Cancer Risk from Dermal Exposure to Toluene Diisocyanate." Poster #2820/P343. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

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Sax, SN; Prueitt, RL; Goodman, JE. 2013. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 8-11.

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Bailey, LA; Goodman, JE; Rhomberg, LR. 2011. "Hypothesis-based Weight-of-evidence Evaluation of Naphthalene: Carcinogenic Hazard Assessment and Mode of Action." Presented at SETAC North America 32nd Annual Meeting, Boston, MA, November 14. 1p.

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Goodman, JE; Rhomberg, LR; Pruiett, RL. 2009. "A Weight-of-evidence Analysis of the Human Carcinogenicity of Styrene." Presented at the Annual Meeting of the American College of Epidemiology, Silver Spring, MD, September 13-15.

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Haber, LT; Rhomberg, LR; Goodman, JE; Dodge, DG; Zhao, QJ; Pagan, I; Foureman, GL. 2007. "Considerations Regarding the Structure and Application of a Pathophysiological Progression Model." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

Dodge, DG; Zhao, QJ; Haber, LT; Goodman, JE; Pagan, I; Foureman, GL; Rhomberg, LR. 2007. "Case Studies for the Development of a Pathophysiological Progression Model: Fatty Liver." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

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Rhomberg, LR; Goodman, JE; McConnell, EE; Sipes, IG; Witorsch, RJ; Slayton, TM; Yu, CJ; Lewis, AS. 2007. "An Updated Weight of the Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A." *Toxicologist* 96(1):427. Abstract No. 2067. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

Beyer, LA; Goodman, JE; Seeley, MR; Slayton, TM; Beck, BD. 2007. "Carcinogenicity Evaluation of Methyl Tert-butyl Ether (MTBE)." *Toxicologist* 96(1):325. Abstract No. 1569. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

Zanetti, KA; Kahn, MA; Bowman, ED; Goodman, JE; Chanock, S; Harris, CC. 2007. "Compromised Complement System Increases Colon Cancer Susceptibility in African-Americans." *Proc. Am. Assoc. Cancer Res.* 48.

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Goodman, JE; Harris, CC. 2005. "GST-T1, p53, and CASPASE-8 Polymorphisms and Colon Cancer Risk." Presented at the Society of Toxicology (SOT) 44th Annual Meeting, New Orleans, LA, March 6-10.

Goodman, JE; Bowman, E; Chanock, S; Harris, CC. 2004. "Arachidonate Lipoxygenase (ALOX) and Cyclooxygenase (COX) Polymorphisms and Colon Cancer Risk." *Proc. Am. Assoc. Cancer Res.* 44.

Goodman, JE; Bowman, E; Chanock, S; Harris, CC. 2004. "ALOX & COX Polymorphisms & Colon Cancer Risk: Association with ALOX-5 G-1753A & G-1700A." Center for Cancer Research Fourth Annual Fellows and Young Investigators Retreat, Williamsburg, VA, March 9-11.

Sullivan, AE; Goodman, JE; Silber, PM; Yager, JD. 2004. "Correlation Between Catechol-O-methyltransferase Genotype and Phenotype." *Toxicologist* 88.

Sullivan, AE; Goodman, JE; Yager, JD. 2003. "Catechol-O-methyltransferase (COMT) and Catechol Estrogens in Breast Cancer." Presented at the 226th National American Chemical Society Division of Toxicology Meeting, New York, NY, September 7-11.

Goodman, JE; Sullivan, AE; He, P; Silber, PM; Yager, JD. 2003. "Correlation Between Catechol-O-methyltransferase Genotype and Phenotype." AACR Molecular and Genetic Epidemiology of Cancer Conference Proceedings, Waikoloa, HI, January 18-23.

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Lavigne, JA; Goodman, JE; Fonong, T; Odwin-DeCosta, S; He, P; Yager, JD. 2001. "The Effects of Catechol-O-methyltransferase Inhibition on Catechol Estrogen Levels and Oxidative DNA Damage in MCF-7 Cells." *Proc. Am. Assoc. Cancer Res.* 42.

Goodman, JE; Lavigne, JA; Hengstler, JG; Helzlsouer, KJ; Yager, JD. 2000. "Catechol-O-methyltransferase Polymorphism Not Associated with Ovarian Cancer." *Proc. Am. Assoc. Cancer Res.* 41.

Chen, JQ; Delannoy, M; Goodman, JE; Lavigne, JA; Odwin, SE; He, P; Yager, JD. 2000. "Enhanced Transcript Levels of Mitochondrial Genes, Respiratory Chain Activity, Bcl-2 Levels and Glutathione Distribution by Ethinyl Estradiol in Female Rat Hepatocytes." *Proc. Am. Assoc. Cancer Res.* 41.

Invited Lectures, Testimony, and Other Presentations

"A Case for Good Epidemiology Practice Guidelines for Regulatory Risk Assessment." Presented at the Environmental Epidemiology Committee Webinar, September 23, 2021.

"Food Safety." Presented at Gradient's Trends 75 Webinar, June 19, 2019.

"Evaluating Adverse Drug Effects in Pharmacoepidemiology Studies." Presented at Gradient's Trends 71 Webinar, February 28, 2018.

"Study Quality and Evidence Integration in the IRIS Process." Presented at the National Academies of Science, Engineering, and Medicine Review of Advances Made to the IRIS Process Workshop, Washington, DC, February 1, 2018.

"Challenges for the Agrochemical Industry." Presented at the International Society of Exposure Science (ISES) Annual Conference, Research Triangle Park, NC, October 17, 2017.

"National Ambient Air Quality Standards." Presented at the Institute for Humane Studies and the Mercatus Center Risk Analysis Seminar, Portland, OR, June 27, 2016.

"Why Epidemiologists Need Toxicologists (and Vice Versa)." Presented at the CropLife America & RISE 2016 Spring Conference, Arlington, VA, April 14, 2016.

"Systematic Review." Presented at the Asphalt Institute Spring Meeting, Nashville, TN, April 13, 2016.

"An Introduction to Meta-analysis." Presented at the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, April 5, 2016.

"Evaluation of Scoring Approaches and Consideration of an Independent Approach." Presented at the 40th Annual Winter Meeting of Toxicology Forum, Washington, DC, February 10, 2016.

"Extrapolation of Controlled Human Study Results to the US Population." Presented at the Society for Risk Analysis Annual Meeting, December 6-9, 2015.

"How a Sensitivity Analysis of Raw Data Would Strengthen EPA's Chlorpyrifos Risk Assessment." Presented at the Society for Risk Analysis Annual Meeting, December 6-9, 2015.

"The Future of Toxicology." Presented at the SPI Food Packaging Summit, November 10, 2015.

"Evaluation of Evidence EPA Cites in Support of the Ozone National Ambient Air Quality Standards for Ozone Proposed Rule." Presented at the 2015 Env-vision Conference, May 12-14, 2015.

"The Scientific Evidence Does Not Support the Administrator's Proposed Conclusion that the Primary Ozone NAAQS Should Be Between 0.065 and 0.070 ppm." Testimony at the US Environmental Protection Agency (EPA) Public Hearing on the Proposed Updates to the National Ambient Air Quality Standards (NAAQS) for Ground-level Ozone, Washington, DC, January 29, 2015.

"Risk-of-bias Analysis: Case Study of Pleural Plaques and Lung Function." Presented at the Society for Risk Analysis Annual Meeting, December 7-10, 2014.

"Is a Stricter Ozone NAAQS Supported by the Science?" Presented at the Association of Battery Recyclers 2014 Fall Meeting, October 16, 2014.

"NexGen: Are We There Yet?" Presented at the 2014 Health Effects Institute Annual Conference, May 6, 2014.

"Hypotheses and Weight-of-evidence Frameworks." Presented at the 53rd Annual Society of Toxicology Meeting, March 23, 2014.

"When an Association Indicates Causation." Presented at the 53rd Annual Society of Toxicology Meeting, March 23, 2014.

"Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Incorporation of Weight-of-evidence Best Practices in the National Ambient Air Quality Standards Review Process." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Bradford Hill Viewpoints and Hypothesis-based Weight of Evidence." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond." Presented at the Harvard Systematic Review Symposium, October 3-4, 2013.

"A Hypothesis-based Weight-of-evidence Approach to Evaluate the Human Carcinogenicity of Isocyanates." Presented at the Isocyanates & Health Conference, April 3, 2013.

"Using Epidemiology to Analyze Neurodevelopmental Toxicity Across Species." Presented at the 52nd Annual Society of Toxicology Meeting, March 14, 2013.

"Designing Case-control Studies." Presented at the New York Medical College School of Health Science & Practice, February 21, 2013.

"Designing Cohort Studies." Presented at the New York Medical College School of Health Science & Practice, February 11, 2013.

"Systemic Reviews and Meta-analysis." Presented in the Use of Expert Elicitation to Inform Decisionmaking Workshop, Society for Risk Analysis 2012 Annual Meeting, San Francisco, CA, December 2012.

"Survival Analysis & Meta-analysis." Presented at the New York Medical College School of Health Sciences & Practice, November 8, 2012.

"Overview of the Controversy Surrounding Bisphenol A Toxicity." Presented at the Biological Relevance and Health Concerns of Genotoxicity Conference, Newark, DE, October 24, 2012.

"Biological & Statistical Interaction." Presented at the New York Medical College School of Health Sciences & Practice, October 11, 2012.

Testimony regarding "EPA's Assessment of Health Benefits Associated with $PM_{2.5}$ Reductions for the Final Mercury and Air Toxics Standards." Presented to the Subcommittee on Energy and Power, United States Congressional Committee on Energy and Commerce American Energy Initiative Hearing, Washington, DC, February 8, 2012.

"Synthesizing Evidence: An Introduction to Systematic Reviews, Meta-analysis, and Expert Elicitation." Presented at the Society for Risk Analysis 2011 Annual Meeting, Charleston, SC, December 2011.

"Why Meta-analyses and Systematic Reviews Come to Different Conclusions About Formaldehyde and Leukemia." Presented at the Society for Risk Analysis 2011 Annual Meeting, Charleston, SC, December 2011.

"The Weight of Evidence Regarding Bisphenol A and Human Health." Presented at the Society for Risk Analysis New England Chapter Meeting, Harvard School of Public Health, Boston, MA, December 2011.

Testimony regarding Air Quality and Children's Health. Presented to the Subcommittee on Clean Air and Nuclear Safety and the Subcommittee on Children's Health and Environmental Responsibility, United States Senate Committee on Environment and Public Works Hearing, Washington, DC, June 8, 2011.

"Bisphenol A and Human Health: What Does the Science Show?" Presented at the Policy of BPA Event, American Enterprise Institute, Washington, DC, June 2010.

"Human Health Risk Assessment." Presented at the Massachusetts Maritime Academy, Buzzards Bay, MA, May 2010.

"The Science Behind the Reconsideration of the Ozone NAAQS." Presented as part of the webinar, How Will EPA's New Ozone Standards Affect Your Community? April 2010.

"Weight-of-evidence Analysis of Reproductive and Developmental Health Effects of Bisphenol A." Presented at the Nypro Bisphenol A Information Event, Clinton, MA, March 2010.

"Everyday Exposures to Bisphenol A Do Not Cause Adverse Health Effects in Humans." Presented at the Harvard Extension School, Environmental Management Program, Cambridge, MA, March 2010.

"New Developments in Exploratory Research on 'Estrogenicity' – Progress Toward Validation of New Endpoints and Testing Methods." Presented at the Society of the Plastics Industry's Food, Drug, and Cosmetic Packaging Materials Committee Winter Conference, Atlanta, GA, December 2009.

"Avoiding Potential Long-term Liability through Risk Assessment for Material Selection." Presented at the 21st Annual Product Liability Conference, University of Wisconsin-Madison, Madison, WI, September 2009.

"Epidemiology and Risk Assessment." Presented at the Annual Meeting of the American College of Epidemiology, Silver Spring, MD, September 2009.

"Risk Assessment Techniques for Materials Selection." Presented as part of the Strategies for Substance Replacement in Products Webinar, May 2009.

"Investigation of Potential Cancer Clusters in Northampton, MA." Presented at the John F. Kennedy School, Northampton, MA, September 2008.

"Did Chemicals in Your Product Cause John Doe's Disease? The Toxicologist Speaks." Presented at the 20th Annual Product Liability Conference, University of Wisconsin-Madison, Madison, WI, September 2008.

"Investigation of Potential Disease Clusters in Northampton, MA: Progress Update." Presented at the Robert K. Finn Ryan Road School, Northampton, MA, October 2007.

"Investigation of Potential Disease Clusters in Northampton, MA." Presented at the Robert K. Finn Ryan Road School, Northampton, MA, May 2007.

"Single Nucleotide Polymorphisms (SNPs), Inflammation and Colon Cancer." Presented at the Cancer Prevention Fellowship Program Seminar Series, NCI, Rockville, MD, February 2004.

"The Epidemiology of Inflammation and Colon Cancer." Presented at the Laboratory of Human Carcinogenesis Meeting, NCI, Bethesda, MD, December 2003.

"Macrophage Migration Inhibitory Factor (MIF) in Inflammatory Bowel Diseases." Presented at the Laboratory of Human Carcinogenesis International Workshop, Bethesda, MD, September 2003.

"Chronic Inflammation and Colon Cancer Risk." Presented at the Cancer Prevention Fellowship Program Seminar Series, NCI, Rockville, MD, June 2003.

Attachment M

Testimony Experience

Expert Testimony
Julie E. Goodman, Ph.D., DABT, FACE, ATS
Last Four Years

Expert #	For:	Plaintiff (P)	Defendant (D)	Case #	Court	District	Date	Legal Proceeding
1	D	Amber, *et al.*	Allied Waste Transportation, Inc., *et al.*	09 L 15741	Circuit Court	State of Illinois, County of Cook	6/16/21	Deposition
2	D	Estate of Wayne D. Vetre	Town of Wells/Maine Municipal Association	218W2797	Worker's Compensation Board		12/14/21	Deposition
3	D	John C. Riegler and Kathi A. Riegler	Ford Motor Company	2:20-cv-00752-RJS-CMR	District Court	District of Utah	4/6/2022	Deposition
4	D	Pamela S. Rud and David Rud	Ford Motor Company	21-L-286	Circuit Court	State of Illinois, County of Madison	5/24/2022	Deposition
5	D	Estate of Eugene G. Hohlfeld, Sr.	Ford Motor Company, *et al.*	18-CV-251	Circuit Court	State of Wisconsin, County of Lacrosse	9/14/2022	Trial
6	D	Estate of Vincent DiFillipo, Sr.	City of Portland and Maine Municipal Association		Worker's Compensation Board		9/29/2022	Deposition
7	D	District of Columbia	Beech-Nut Nutrition Company	2021 CA 001292B	Superior Court	District of Columbia	3/2/2023	Deposition
8	D	Citizens for the Environment	Elcon Recycling Center (2003) Ltd., *et al.*	CA 36568-07-19	District Court	Haifa, Israel	5/15/2023; 5/17/2023	Trial
9	D	Vicki Lee and the Estate of Steven A. Lee	Ford Motor Company	2019CV000344	Circuit Court	State of Wisconsin, County of Grant	6/1/2023	Deposition
10	D	Robert Collins	Allied Fluid Products Corp., *et al.*	22CV021614	Superior Court	State of California, County of Alameda	6/5/2023	Deposition
11	D	Bryan Dick-Ipsen	Tri-Supply Co., *et al.*	2018-L-011367	Circuit Court	State of Illinois, Cook County	8/10/2023	Deposition
12	D	Ricky Bush, *et al.*	Clean Harbors Colfax, LLC	1:22-cv-02026-DDD-JPM	District Court	State of Louisiana, Alexandria Division	10/2/2023	Deposition
13	D	In Re: New Indy Emissions Litigation		21-CV-01480-SAL, 21-CV-01704-SAL	District Court	District of South Carolina, Rock Hill Division	10/30/2023	Deposition
14	D	William Grit	Koch Remediation and Environmental Services, LLC; *et al.*	2021-CV-000527	District Court	State of Kansas, County of Shawnee	2/16/2024	Deposition
15	D	Yehoshua Klein, *et al.*	Oil Refineries Ltd., *et al.*	CA 11278-10-19	District Court	Tel Aviv, Israel	3/12/2024	Trial
16	D	James S. Diede and Jeanne Diede	A.O. Smith Corporation., *et al.*	Civil Action No. 23-0274	Superior Court	State of Massachusetts, County of Middlesex	6/12/2024	Deposition
17	D	Stephen P. Sutton, *et al.*	W. L. Gore & Associates, Inc.	Civil Action No. 1:22-cv-1471	District Court	State of Maryland	9/11/2024	Deposition
18	D	FTCA Flint Water Cases		Civil Action No. 4:17-cv-11218	District Court	Eastern District of Michigan, Southern Division	9/19/2024; 10/9/2024	Deposition
19	D	Bruce S. Wright and Louis K. Wright	Cummins Inc., *et al.*	Civil Action No. 1:23-cv-10496	District Court	District of Massachusetts	11/20/2024	Deposition