Exhibit 94

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

Prepared by



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Abbreviations

1,1,1-TCA	1,1,1-Trichloroethane
ACS	American Cancer Society
AML	Acute Myeloid Leukemia
ARRIVE	Animal Research: Reporting of *In Vivo* Experiments
ATS	Academy of Toxicological Sciences
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body Mass Index
CEO	Chloroethylene Oxide
CI	Confidence Interval
CIR	Confidence Interval Ratio
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DCE	Dichloroethylene
DNA	Deoxyribonucleic Acid
GLP	Good Laboratory Practice
GSH	Glutathione
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
i.p.	Intraperitoneal
IRIS	Integrated Risk Information System
IRR	Incidence Rate Ratio
JEM	Job Exposure Matrix
KCC	Key Characteristics of Carcinogens
LNT	Linear No-Threshold
MDS	Myelodysplastic Syndrome
mmHg	Millimeters of Mercury
MoA	Mode of Action
MTD	Maximum Tolerated Dose
NAM	National Academy of Medicine
NASEM	National Academies of Sciences, Engineering, and Medicine
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NOCCA	Nordic Occupational Cancer Study
NPTCC	Non-Papillary Transitional Cell Carcinoma
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OR	Odds Ratio
PCE	Perchloroethylene
PCMR	Proportionate Cancer Mortality Ratio
PIR	Proportionate Incidence Ratio

PMR	Proportionate Mortality Ratio
ppb	Parts Per Billion
ppm	Parts Per Million
PTCC	Papillary Transitional Cell Carcinoma
PVC	Polyvinyl Chloride
RCC	Renal Cell Carcinoma
RR	Relative Risk
SciRAP	Science in Risk Assessment and Policy
SIR	Standardized Incidence Ratio
SMHS	Shanghai Men's Health Study
SMR	Standardized Mortality Ratio
SRRE	Summary Relative Risk Estimate
SSA	Social Security Administration
SWHS	Shanghai Women's Health Study
TCA	Trichloroacetic Acid
TCC	Transitional Cell Carcinoma
TCE	Trichloroethylene
trans-1,2-DCE	*trans*-1,2-Dichloroethylene
TVOC	Total Volatile Organic Compounds
US EPA	United States Environmental Protection Agency
U-TCA	Urinary Trichloroacetic Acid
UTUC	Upper Tract Urothelial Carcinoma
VC	Vinyl Chloride
VHA	Veterans Health Administration
VHL	Von Hippel-Lindau Gene
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 kidney cancer in individuals that worked or resided at Camp Lejeune.

I analyzed relevant epidemiology and toxicology literature to assess whether it generally supports a causal association between exposure to these chemicals and kidney cancer at Camp Lejeune or more generally. My opinions are based on a review of the published scientific literature to date, 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 kidney cancer risks 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 kidney 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 mode-of-action (MoA) evidence regarding TCE and kidney 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 each of the five chemicals and kidney 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 kidney cancer risks among Marines or Navy personnel stationed at Camp Lejeune or civilian workers on base. The methods used to recruit or 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 kidney 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, as noted by NRC (2009), "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, in general, do not provide evidence that exposures to TCE, PCE, benzene, or vinyl chloride can cause kidney cancer.

Overall, 1) Camp Lejeune epidemiology studies are not of high quality and most analyses do not provide evidence of associations between working or living at Camp Lejeune, or TCE, PCE, benzene, or vinyl chloride exposures in drinking water at Camp Lejeune, and kidney cancer and 2) animal and mechanistic

studies do not provide evidence of causation in humans for TCE, PCE, benzene, or vinyl chloride, 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 kidney 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 1,1,1trichloroethane (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.

A small increase in kidney tumors has been found in male rats in a study that the investigators concluded was equivocal because dosed groups had reduced survival *vs*. vehicle controls. Kidney cancer was not increased in TCE-treated female rats, or in mice or hamsters of either sex in other studies. There is some evidence supporting a genotoxic MoA mediated by reactive metabolites of TCE; however, there is uncertainty regarding whether TCE metabolism in humans is sufficient to cause kidney cancer.

Most risk estimates reported for TCE exposure and kidney cancer in epidemiology studies were between 1 and 2, and most of those high in magnitude had wide confidence intervals (CIs). Various methodological limitations could have biased epidemiology study results (*e.g.*, inappropriate comparison groups, indirect exposure assessments, and residual confounding). Although study limitations make the interpretation of study results difficult (particularly with respect to exposure estimates), considering the relative consistency of risk estimates >1, and the results of Charbotel *et al.* (2006) (which are based on robust exposure estimates according to US EPA, 2011), the epidemiology evidence provides support for an association between kidney cancer and very high occupational TCE exposures (*e.g.*, >335 ppm-yr in Charbotel *et al.*, 2006).

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.

Several epidemiology studies and animal bioassays have evaluated PCE exposure and kidney cancer. Epidemiology studies reported a wide range of risk estimates, most of which were null, and the few statistically significant associations were 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 their results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). No chronic animal study reported a statistically significant increase of kidney tumors associated with oral or inhalation exposure to PCE. While some MoAs have been proposed, there is no MoA for kidney cancer in humans with sufficient scientific support.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between PCE exposure and kidney 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 animal bioassays have evaluated benzene exposure and kidney cancer. There is no evidence that benzene causes kidney cancer in animal models, and epidemiology evidence does not support an association. Most epidemiology studies reported risk estimates around 1 and, while some statistically significant associations were reported in a few studies, they were based on indirect or non-specific exposure measurements with no clear, consistent exposure-response trends. In addition, the epidemiology evidence is based on studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. Animal bioassays do not provide evidence that benzene can cause kidney cancer and there is no biologically plausible MoA by which benzene can cause kidney cancer.

Because most of the epidemiology studies are not of high quality and most analyses do not support associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between benzene exposure and kidney 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 epidemiology studies and animal bioassays have evaluated vinyl chloride exposure and kidney cancer. Vinyl chloride does not cause kidney cancer in animal models, and epidemiology evidence does not support an association. Most epidemiology studies reported risk estimates that were null and close to 1. Statistically significant associations were not consistently reported within or across studies, and none were specific to vinyl chloride. In addition, epidemiology evidence is based on studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding.

Because the epidemiology studies are not of high quality and most analyses do not support associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between vinyl chloride exposure and kidney 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, 2020c). 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 kidney 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.

Overall, government and international agencies conclude that there is evidence to support an association between TCE and kidney cancer in humans, primarily based on studies where participants had high occupational exposures. These agencies conclude that the scientific evidence does not support a likely association with PCE or an association with benzene at all. Most agencies did not discuss kidney cancer in their reviews of vinyl chloride; US EPA (2000a) stated, "No evidence for induction of kidney tumors in humans by VC has been reported." 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

While TCE does not cause kidney cancer in animal bioassays, and most epidemiology studies are not of high quality, there is epidemiology evidence supporting an association between very high occupational TCE exposures (*i.e.*, >335 ppm-yr) and kidney cancer. Evidence does not support a causal association between PCE, benzene, vinyl chloride, or *trans*-1,2-DCE exposure and kidney cancer. 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 kidney 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 kidney 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.

Notes:
HR = Hazard Ratio; IRR = Incidence Rate Ratio; OR = Odds Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio.
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*. (2024a), "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

[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).

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 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 $\geq \sim 2.5$) 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*. (2024a) 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*. (2024a) 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*. (2024a) 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 studies (*e.g.*, Bove 2024a, b) and 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. Because these types of studies do not have individual-level exposure data, they cannot provide direct evidence for a specific exposure-outcome association.

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. In 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]

[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.

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 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, 2005). 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, 2005). This is because regulators do not estimate the likelihood of health effects actually occurring in a population or an individual (US EPA, 2004; ATSDR, 2018a). 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 an 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 kidney cancer. I limited my epidemiology review to studies that evaluated kidney cancer in adult populations. 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 kidney 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 kidney 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,

[5] As noted by ATSDR (2024a), which also excluded epidemiology studies of benzene exposures in ambient air, there is "great uncertainty about causality in 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."

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.

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 (>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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures ▪ ≤5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Considered time-varying nature of relevant covariates (*e.g.*, smoking)	▪ Did not control for or consider age, sex, race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, 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 (*e.g.*, smoking)
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 data), neither type of estimate is likely to be accurate and reliable with respect to individual exposures.

[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.

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 in which 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, 2024b).

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

Because kidney 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 kidney cancer mortality to be weaker than those that evaluated kidney 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, obesity, hypertension, genetic factors, a family history of kidney cancer, and diabetes are risk factors for kidney cancer (Mayo Clinic, 2022; Scelo and Larose, 2018; ACS, 2020a; Tseng, 2015; Habib *et al*., 2012; Inoue *et al*., 2006), while alcohol consumption is inversely associated with kidney cancer risk (Song *et al*., 2012). All of these factors should be considered in studies of kidney cancer, even if they are not confounders, because including them in statistical models increases the precision of effect estimates without increasing bias (Velentgas *et al*., 2013). I considered studies to be stronger if they controlled for at least some of these factors in the study design or analysis.

Also, the evidence regarding chemical exposures and kidney cancer is inconsistent, but because dry cleaners and other industrial occupational exposure groups were likely exposed to a variety of chemicals, including solvents, stronger studies consider all potential chemical exposures in analyses.

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 kidney cancer development (<4 years) (CDC, 2015) are weaker than those with sufficient time between the exposure and kidney 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), 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) 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[8]: 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 carcinogenicity studies, the background cancer 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.

[8] I did not systematically review *in vitro* data.

Parameter	Strength	Weakness
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 Assessment	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 assessment 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 to 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 a 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 Assessment

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 kidney 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; Freeman, 2024; Bird, 2024; Mallon, 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 kidney 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 1 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; US EPA, 2005). 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.
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 kidney 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 (1965) noted that there might be occasions when information on biological plausibility is not available. 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?

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)	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.

Notes:
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 (2008) 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 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 more 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 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, 2020a), or did not draw any conclusions regarding this potential association (ATSDR, 2019a; 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 kidney 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 (2017) Hierarchies of Evidence for Causation

Level of Evidence	IOM (2008)[a]	ATSDR (2017a)[a]
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 Hill's 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).
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

Level of Evidence	IOM (2008)[a]	ATSDR (2017a)[a]
		interest has been found and in which chance and biases can be ruled out with reasonable confidence.
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.

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; IOM = Institute of Medicine.
(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). Each carcinogen impacts specific biological pathways and can only cause specific cancer types (ACS, 2019b; Meek *et al*., 2014; US EPA, 2005). For example, radiation from sun exposure has been shown to cause various types of skin cancer (Berwick *et al*., 2005; Fartasch *et al*., 2012) but not any other type of cancer.

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 tumors. 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." It is also important to note that 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).

In addition, for a substance to cause cancer, there must be sufficient exposure to that substance (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):

> 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. (NRC, 2001)

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, 2015a). 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 (NCI, 2015b; 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), "[H]aving 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, 2015a). 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, 2015a). Other common risk factors for cancer include radiation and extreme sun exposure (Johns Hopkins Medicine, 2019).

4.2 Kidney Cancer

Kidney cancers start in the kidneys, which remove excess water, salt, and waste products from the blood (ACS, 2020b). There are several types of kidney cancer. Renal cell carcinoma (RCC), which is the most common type of kidney cancer, forms in the lining of the very small tubes in the kidney. Approximately 90% of kidney cancers are RCCs (ACS, 2020b). There are several subtypes of RCC; ~70% of RCC cases are clear-cell RCC and ~10% are papillary RCC (ACS, 2020b). Other types of kidney cancer include transitional cell carcinoma (*i.e*., urothelial carcinoma), comprising 5-10% of all kidney cancers; Wilms tumor (*i.e*., nephroblastoma), which occurs primarily in children; and renal sarcoma, comprising <1% of all kidney cancers (ACS, 2020b).

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, 2020b). 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, the toxicity and epidemiology studies I identified do not differentiate between TCC of the bladder and upper urinary tract. Therefore, I evaluate urothelial cell cancers in my bladder cancer report (Goodman, 2025).

NCI estimated that, in 2023 in the US, there would be 81,800 new cases and 14,890 deaths due to kidney and renal pelvis cancer (*i.e.*, cancer forming in the center of the kidney, where urine collects) combined. Kidney cancer is expected to represent approximately 4.2% of all new cancer cases in 2023 in the US and, in 2020, there were an estimated 628,355 people in the US living with kidney and renal pelvis cancer. NCI reported an overall lifetime risk of being diagnosed with kidney cancer of 1.8% for people in the US, based on data from 2016-2020. Kidney cancer is more common in men than women. For the period of 2016-2020, the overall age-adjusted incidence rate was 23.5 per 100,000 men and 11.7 per 100,000 women in the US. About 55.8% of all new US kidney cancer cases are diagnosed in people between the ages of 55 and 74 years, with a median age at diagnosis of 65 years (NCI, 2023).

Risk factors for transitional cell carcinomas, which form in the lining of the renal pelvis, include cigarette smoking, a personal history of bladder cancer, taking certain pain medications frequently (*e.g.*, phenacetin), and exposures to certain dyes and chemicals, such as those used to make leather goods, textiles, plastics, and rubber (ACS, 2020b; NCI, 2024b). Most Wilms tumors have no clear cause, but certain factors have been identified that affect risk: younger age, race (Black), sex (female), a family history of Wilms tumors, certain genetic syndromes (*e.g.*, WAGR syndrome, Denys-Drash syndrome, Frasier syndrome, and Beckwith-Wiedemann syndrome), and certain birth defects (*e.g.*, aniridia [*i.e.*, complete or partial lack of the iris], hemihypertrophy, cryptorchidism, and hypospadias) (ACS, 2018). The risk factors for renal sarcomas, which form in the blood vessels or connective tissues of the kidney, are unclear due to the rarity of this cancer (Poombal *et al*., 2023; ACS, 2020b).

RCC has several risk factors, including genetic factors and lifestyle factors (*e.g.*, smoking) (ACS, 2020a). Among demographic risk factors, being male, older, African American, and taller make it more likely that an individual will develop RCC (Scelo and Larose, 2018; ACS, 2020a). It has been estimated that smoking tobacco increases the risk of developing RCC by ~30% among current smokers and 15% among former smokers (Scelo and Larose, 2018), potentially contributing to about one-third of all cases of RCC (Medscape, 2020). There is overwhelming evidence from large, prospective cohorts that excess body weight is associated with an excess risk of kidney cancer in a linear manner (Scelo and Larose, 2018; Wilson and Cho, 2016). Being obese (body mass index [BMI] of ≥30) has been estimated to increase risk by 72-77% (Scelo and Larose, 2018; Liu *et al*., 2018; Parkin and Boyd, 2011; Wang and Xu, 2014).

Among medical and genetic risk factors, hypertension is known to predispose a person to kidney cancer. Several prospective cohort studies have reported a dose-response relationship between blood pressure and kidney cancer risk (Scelo and Larose, 2018; Chow *et al*., 2000). Hypertension has been shown to act independently from obesity in increasing kidney cancer risk (Scelo and Larose, 2018; Chow *et al*., 2000). There is also accumulating epidemiology evidence linking diabetes mellitus to RCC (Tseng, 2015; Habib *et al*., 2012; Inoue *et al*., 2006). Finally, alcohol consumption is inversely associated with kidney cancer risk (Song *et al*., 2012).

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 kidney cancer risks in US Marines and Navy personnel or civilian employees at Camp Lejeune. The characteristics and results of these studies are shown in Attachment B. The quality of each study is described in Attachment C. Below, I provide brief summaries of these 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 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; Bove *et al*., 2024a) had high retention and low loss to follow up, largely because of their reliance on historical records for enrollment and outcome ascertainment. 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 studies (Bove *et al*., 2014a,b; Bove *et al*., 2024a,b) relied on historical records, so selection bias was unlikely. ATSDR (2018b) actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated:

> [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 kidney cancer risks in Camp Lejeune populations to risks in Camp Pendleton populations without consideration of chemical-specific exposures or doses. Two of the studies (Bove *et al*., 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 modify their exposure potential (*e.g*., water consumption/exposure). Bove *et al*. (2024a,b) considered disease risk by duration of assignment on base, but this did 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*. (2014a,b) and ATSDR (2018b) 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.

Bove *et al*. (2014b) estimated risks in Camp Lejeune civilian employees with ≥ median exposures to each chemical compared to those with < median exposures. For all four chemicals, all cases had ≥ median exposures, resulting in risk estimates that are difficult to interpret (*e.g*., ∞). Finally, Bove *et al*. (2014a) and ATSDR (2018b) reported near perfect correlations between the TCE, benzene, vinyl chloride, and total VOC categorical exposure variables among Marines and Navy personnel. For civilian employees, Bove *et al*. (2014b) reported high correlations between TCE, PCE, benzene, and vinyl chloride, while ATSDR (2018b) 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 (2018b) 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). Nondifferential exposure error is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020) or categories formed from continuous exposure measurements (Flegal *et al*., 1991), similar to what was modeled and estimated in Bove *et al*. (2014a) and ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null.

5.1.3 Outcome Assessment

Bove *et al*. (2014a,b; 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 (2018b) 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 *et al*. studies (2014a,b; 2024a,b) used reliable sources to identify cases or deaths (*i.e*., Social Security Administration [SSA], commercial tracing services, National Death Index, cancer registries). ATSDR (2018b) 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 kidney cancer is not always fatal,

analyses evaluating incidence are more informative than those evaluating mortality. Bove *et al*. (2024a,b) evaluated kidney cancer risk by subtype: renal cell and clear cell carcinoma, renal cell carcinoma, clear cell only, papillary, and not otherwise specified.

5.1.4 Covariates

All ATSDR (2018b) analyses controlled for age, while analyses among Marines and Navy personnel also controlled for sex. All four Bove *et al.* studies (2014a,b; 2024a,b) controlled for age, sex, and race. Bove *et al*. (2014a) also controlled for rank and education in internal analyses and comparisons with Camp Pendleton, while Bove *et al*. (2014b; 2024a,b) also controlled for education and occupation (blue *vs.* white collar) as a proxy for other chemical exposures in internal analyses and comparisons with Camp Pendleton among civilian employees. Bove *et al*. (2014b; 2024a,b) also controlled for calendar period in some analyses. No Camp Lejeune study controlled for other important covariates, including smoking, obesity, hypertension, genetic factors, family history of kidney cancer or diabetes.

Four of the Camp Lejeune studies considered smoking indirectly. Bove *et al*. (2014a,b) evaluated whether the risk of smoking-related diseases that were not associated with solvents were different in the Camp Lejeune and Camp Pendleton populations. Bove *et al*. (2014a) concluded that the effects of confounding from smoking on risk estimates in their study of Marines and Navy personnel were <10%, because the "HRs for the other smoking-related diseases (chronic obstructive pulmonary disease [COPD] and cardiovascular disease) were less than 1.10, and HRs for diseases that are both smoking and solvent related (*e.g.*, laryngeal and oral cancers) were less than 1.00." Similarly, Bove *et al*. (2014b) 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%." Despite these calculations, the degree to which smoking contributed to these smoking-related diseases in study participants is unknown, and this analysis is not informative with respect to the degree of confounding from smoking in other 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." He conducted these analysis for kidney cancer in both studies and concluded that confounding by smoking is likely to be minor However, bias estimates were based on a series of assumptions that were not validated (*i.e*., true risk of kidney cancer due to smoking; the prevalence of smoking in Camp Pendleton and Camp Lejeune; a uniform distribution of smoking among the populations), so the results were uninterpretable.

Finally, the amount of missing covariate data reported varied by study, but none reported having no missing data, 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 (2024b) and Bove *et al*. (2014a,b) 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 (2018b) also did not consider disease latency in its 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*. (2014a)

Bove *et al*. (2014a) retrospectively evaluated kidney 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 42 kidney cancer deaths in this cohort, which was not more than expected compared to the general US population (SMR = 1.16, 95% CI: 0.84-1.57). The risk of kidney cancer death was also similar in Camp Lejeune Marines and Navy personnel compared to that in 154,969 Marines and Navy personnel at Camp Pendleton when a 10-year lag between exposure and outcome was considered (HR = 1.35, 95% CI: 0.84-2.16).

Bove *et al*. (2014a) 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 kidney cancer death associated with increasing cumulative exposure to any chemical (HR range: 0.95-1.50). Similarly, there was no statistically significant increased risks of kidney 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 (TCE, PCE, vinyl chloride), or <2 μg/L-month (benzene) in this Camp Lejeune cohort (HR range: 1.21-1.54). Risk estimates did not increase in a linear pattern for any chemical (*i.e*., the highest risk estimate was in the lowest 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 did not report any statistically significant trends with kidney cancer mortality.

5.2.2 Bove *et al*. (2014b)

Bove *et al*. (2014b) retrospectively evaluated kidney 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 seven kidney cancer deaths in this cohort, which was not more than expected compared to the general US population (SMR = 1.30, 95% CI: 0.52-2.67). There was no difference between the risk of kidney cancer death among Camp Lejeune civilian employees compared to that in 4,690 civilian employees at Camp Pendleton (HR = 1.92, 95% CI: 0.58-6.34).

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. In analyses based on categorized maximum cumulative exposure levels (< or ≥ median) among Camp Lejeune employees, all seven kidney cancer cases occurred in subjects with median or above exposures of TCE, PCE, and vinyl chloride, so no risk estimates were calculated. For benzene, there was no statistically significant difference in kidney cancer mortality risks between groups. The authors also evaluated exposure-response relationships using continuous and $\log_{10}$ continuous cumulative exposure models for each chemical and did not report any statistically significant trends with kidney cancer mortality.

5.2.3 ATSDR (2018b)

ATSDR (2018b) retrospectively evaluated kidney cancer incidence among 50,684 Marines and Navy personnel and 2,168 civilian employees who were stationed between 1975 and 1985 or employed between 1972 and 1985 at Camp Lejeune and potentially exposed to contaminated drinking water on base. A health survey was administered between 2011 and 2012 that collected information on cancer and lifestyle and demographic factors. Between 1979 and 2008, there were 192 kidney cancer cases among Marines and Navy personnel at Camp Lejeune, which was similar to that expected compared to Camp Pendleton Marines and Navy personnel (OR = 1.31, 95% CI: 0.86-1.99). Among civilian employees, 20 cases of kidney cancer were reported, which was not more than expected compared to civilian employees at Camp Pendleton (OR = 1.52, 95% CI: 0.69-3.35).

The categorized levels (low, medium, high) of TCE, benzene, vinyl chloride, and total volatile organic compounds (TVOC) for the Marines and Navy personnel analyses were almost completely correlated in this study ($\gamma = 0.99$), so results were only presented for TCE and PCE ($\gamma = 0.88$). For male Marines and civilian employees, cut points at the 50th ("medium exposure") and 90th ("high exposure") percentiles of estimated TCE and PCE exposure levels were used in statistical analyses. For female Marines, cut points at the 75th and 90th percentiles were used to categorize exposures because the 50th percentile was 0 ppb). Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune did not have a statistically significant increased risk of kidney cancer incidence associated with increasing cumulative exposure to TCE (OR range: 0.90-1.45). When comparing those with medium TCE exposure to those with low TCE exposure in the Camp Lejeune cohort, a small, statistically significant increase in the risk of kidney cancer incidence was reported (OR = 1.45, 95% CI: 1.05-2.00), but this was not the case when risks associated with high TCE exposure were compared to low TCE exposure (OR = 1.55, 95% CI: 0.95-2.54).

Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune did not have an increasing kidney cancer risk with increasing cumulative PCE exposure (OR range: 0.88-1.79). Statistically significant increases in risk for kidney cancer incidence were reported in comparisons of Marines and Navy personnel at Camp Lejeune with medium PCE exposures to those with low exposure (OR = 1.43, 95% CI: 1.02-2.00) or high exposures (OR = 2.01, 95% CI: 1.29-3.13).

The correlation between TCE and PCE in civilian employees was approximately equal to one, so the results were reported for TCE and PCE combined. Compared to those at Camp Pendleton, civilian employees at Camp Lejeune had a statistically significant increased risk of kidney cancer incidence in the highest exposure category (OR = 13.92, 95% CI = 5.09-38.10); this was based on nine cases and the wide CI indicates this is not a stable estimate. There was also a pattern of increasing risk with increasing exposure (*i.e.*, those in the high exposure category had a higher risk than those in the low or medium exposure categories), but a p-trend value was not provided. A statistically significant increased risk of kidney cancer incidence was also noted when comparing civilian employees at Camp Lejeune with medium TCE and PCE exposures to those with low exposure (OR = 5.34, 95% CI: 1.38-20.6) based on eight cases. Similarly, when comparing those with high TCE and PCE exposure to those with low exposure, a large, unstable risk estimate was reported (OR = 41.54, 95% CI: 0.30-76.10), but this range is very wide and includes 1. The risk of incident kidney 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 chemicals were not likely accurate or reliable.

5.2.4 Bove *et al*. (2024a)

Bove *et al*. (2024a) retrospectively evaluated kidney 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. Between 1979 and 2018, there were 139 kidney cancer deaths among Marines and Navy personnel at Camp Lejeune, which was expected based on rates in the US general population (SMR = 1.11, 95% CI: 0.93-1.31) and similar to that among Camp Pendleton Marines and Navy personnel (HR = 1.21, 95% CI: 0.95-1.54). When the risk of kidney cancer mortality was evaluated among all personnel ever stationed at Camp Lejeune, a significant increase in risk was only reported when compared to personnel at Camp Pendleton (RR = 1.22, 95% CI: 1.03-1.45), but not when compared to the general US population (SMR = 1.13, 95% CI: 1.00-1.27). There were 24 kidney cancer deaths among civilian employees, which was what was expected compared to the US general population (SMR = 1.16, 95% CI: 0.74-1.73) and similar to that in Camp Pendleton civilian employees (HR = 1.44, 95% CI: 0.73-2.84).

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 kidney cancer death associated with any duration of assignment (HR range: 1.04-1.33), and there was no increase in risk with increasing duration of assignment (*i.e.*, the lowest risk was in the high exposure category). Similarly, compared to those at Camp Pendleton, civilian employees at Camp Lejeune did not have a statistically significant increased risk of kidney cancer death associated with any duration of assignment (HR range: 1.36-1.68), and there was no increase in risk with increasing duration of assignment (*i.e.*, risks in the low and medium exposure categories were similar).

5.2.5 Bove *et al*. (2024b)

Bove *et al*. (2024b) retrospectively evaluated kidney and renal pelvis 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. Between 1996 and 2017, there were 710 kidney and renal pelvis cancer cases among Marines and Navy personnel at Camp Lejeune, which was similar to the incidence among Camp Pendleton Marines and Navy personnel (HR = 1.06, 95% CI: 0.95-1.18). The results for kidney cancer subtypes (*i.e.*, renal cell and clear cell carcinoma, RCC, clear cell, and papillary) were very similar to the results for all 710 kidney and renal pelvis cancers combined (HR range: 0.97-1.18). Compared to those at Camp Pendleton, Marines and Navy personnel stationed at Camp Lejeune between 1975 and 1985 did not have any differences in risk for all kidney and renal pelvis cancers and kidney cancer subtypes when duration of assignment was considered. For all kidney and renal pelvis cancer and kidney cancer subtypes, there was no pattern of increasing risk with increasing duration of assignment (*i.e.*, the highest risk estimates were often in the shortest duration of assignment categories).

There were 58 kidney and renal pelvis cancer cases among civilian employees, which was similar to that in Camp Pendleton civilian employees (HR = 1.12, 95% CI: 0.76-1.67). The results for kidney cancer subtypes were similar to the results for all 58 kidney cancers combined (HR range: 0.51-1.48). Compared to those at Camp Pendleton, civilian employees at Camp Lejeune did not have an increased risk of kidney and renal pelvis cancer incidence with increasing duration of employment. The results for each kidney cancer subtype based on duration of employment were also similar to the results for all kidney cancers combined.

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 kidney 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."

5.3 Conclusions

Five studies have evaluated kidney cancer risks among Marines and 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 kidney 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 several potential confounders in all studies, and the potential for selection bias in ATSDR (2018b). There are no toxicity or mechanistic studies of Camp Lejeune drinking water, 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 kidney cancer.

Because the Camp Lejeune epidemiology studies are not of high quality and most analyses do not support 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 kidney cancer.

6 TCE and Kidney Cancer

In this section, I describe epidemiology and toxicity studies that assessed TCE exposure and kidney cancer, and government and other agency reviews of this evidence. The scientific evidence is not consistent. TCE does not cause kidney cancer in most animal bioassays, while epidemiology evidence provides some support for an association between TCE and kidney cancer. The strongest epidemiology evidence comes from Charbotel *et al.* (2006), which has high-quality exposure estimates. This study found an association only at very high occupational TCE exposures (*i.e.*, >335 ppm-yr). I conclude that the epidemiology evidence provides support for an association between kidney cancer and very high occupational TCE exposures.

6.1 Epidemiology

6.1.1 Overview

I identified 33 cohort studies (in 26 unique populations), 27 case-control studies (in 25 unique populations), three meta-analyses, and one pooled study that evaluated TCE exposure and kidney cancer. The majority of studies were conducted in Europe and North America, and the rest were conducted in Australia, New Zealand, and Taiwan. I review here all studies in populations at Camp Lejeune if TCE 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 and quality below and in Attachments D and C, Tables D.1, D.3 and C.1. Cohort, case-control and pooled and meta-analysis study results are discussed in Section 6.1.2 and in Attachment D, Tables D.2, D.4, and D.5, respectively. Epidemiology evidence is integrated with experimental evidence in Section 6.3.

6.1.1.1 Study Population

In all cohort studies, exposed and unexposed participants were selected from appropriate source populations. Individuals with and without kidney 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.*, Brownson [1988] used hospital-based controls). Most cohort studies reported low rates of loss to follow-up and exclusion (<20%). However, many of the case-control studies reported low participation rates (<80%), 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 an assessment of selection bias difficult. As discussed in Section 5, ATSDR (2018b) actively recruited participants *via* mail surveys; at the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) noted that this 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 of the cohort and case-control studies was the manner by which exposures were estimated. The epidemiology studies examining TCE exposure and kidney cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, cardboard factory workers in Henschler *et al*., 1995a). Almost all studies estimated individual exposures to TCE in an indirect manner, usually based on a JEM, self-reported exposures, or occupational categories (*e.g.*, mechanics), all of which were likely subject to varying degrees of exposure misclassification (*e.g.*, self-reported TCE exposures in Brüning *et al*., 2003). Several studies had data on a TCE metabolite (TCA) in urine (*e.g.*, Hansen *et al*., 2001) or TCE in water (*e.g.*, ATSDR, 2018b). Urinary TCA (U-TCA) is not specific to TCE and only reflects recent exposure; some studies only used U-TCA to characterize whether a population was ever exposed to TCE rather than as a direct measurement of exposure (*e.g.*, Anttila *et al*., 1995; Hansen *et al*., 2001). Most of the studies that measured TCE in water did not link these measurements to individual water consumption data. Aside from Hansen *et al*. (2001) and Charbotel *et al*. (2006), which discussed U-TCA or air monitoring data, no other studies linked air concentrations to individuals.

US EPA (2011) concluded that Charbotel *et al*. (2006) and Moore *et al*. (2010) had the most reliable exposure estimates. Charbotel *et al*. (2006) studied a population with a documented high probability of TCE exposure based on U-TCA measurements and the predominant industry in the area (screw-cutting). The study had a detailed exposure assessment that allowed for a task-based exposure matrix using data from questionnaires, and either U-TCA or air monitoring data provided information for several exposure metrics (*e.g.*, cumulative, peak) and multiple exposure categories (*e.g.*, low, medium, high, +/- peaks) (US EPA, 2011; Fevotte *et al*., 2006). Moore *et al*. (2010) evaluated TCE and kidney cancer in a population with a high incidence of kidney cancer without a clear cause, and industrial hygienists assessed different levels of exposure (*e.g.*, any, duration, cumulative, intensity) based on participants' self-reported occupational histories. US EPA (2011) concluded that Charbotel *et al*. (2006) likely provided the most accurate characterization of exposure because the authors "relied on a task-exposure matrix based on decades of measurements from the Arve Valley workshops." Moore *et al*. (2010) was deemed slightly less accurate because "the cumulative exposure estimates were assessed by experts based on categorical metrics for frequency and intensity of exposure and not continuous measures" (US EPA, 2011).

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on ATSDR (2007a, 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). None of these studies 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*. (2014a,b) and ATSDR (2018b), 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 after kidney cancer had been diagnosed (*e.g.*, Vamvakas *et al*., 1998). 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 can occur when cases recall 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 of the studies did not consider the frequency, duration, or intensity of potential exposures. The studies that accounted for exposure levels did so based on modeled contamination in drinking water (with no individual consumption data – *e.g.*, ATSDR, 2018b), JEMs, or duration of employment. The most common method of assessing exposure level in both cohort and case-control studies was based on duration of employment (*e.g.*, Raaschou-Nielsen *et al.*, 2003; Zhang *et al.*, 2004). When exposure characterization is based on methods that are already highly susceptible to exposure misclassification, such as self-reported exposures (*e.g.*, Zhang *et al.*, 2004) or crude employment categories (*e.g.*, employment at blue collar companies in Raaschou-Nielsen *et al.*, 2003), basing exposure on duration of employment without information on exposure dose increases the potential for further misclassification. Because of this, I considered studies that estimated intensity of exposures (*e.g.*, cumulative exposures in Charbotel *et al.* [2006]) to be of higher quality than those that only considered frequency or duration of exposure.

6.1.1.3 Outcome Assessment

Kidney cancer data were obtained or confirmed using reliable and complete methods in most cohort and case-control studies. For example, 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 in medical facilities. A few studies may have had incomplete ascertainment of cases, namely when relying on self-report without another source of identification such as a registry to identify cases who did not self-report or who were deceased (*e.g.*, ATSDR, 2018b).

6.1.1.4 Covariates Considered

All epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. Most cohort studies controlled for age and sex, while other variables were controlled for less consistently (*e.g.*, race, smoking, obesity) and others were rarely controlled for (*e.g.*, other potential chemical exposures, alcohol consumption). This is likely a reflection of the fact that many of these studies were retrospective and relied on company records or census data that did not capture information on these key variables. 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.*, diabetes status or smoking). Case-control studies generally controlled for a larger number of important covariates than the cohort studies, but most were still missing key variables, including other possible co-exposures. Most of the cohort and case-control 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 prior to the outcome, but many did not consider an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥4 years for kidney cancer; CDC [2015]). Most of the case-control studies considered exposures prior to the outcome, but most did not appropriately consider a latency period.

6.1.2 Study Results

Overall, cohort and case-control studies reported a wide range of risk estimates for TCE and kidney cancer. Risk estimates ranged from 0.31-41.54, except for two studies (Bove *et al.*, 2014b; Silver *et al.*, 2014).

Bove *et al*. (2014b) reported an HR = ∞ comparing kidney cancer mortality in Camp Lejeune civilian employees with ≥ median cumulative TCE exposures compared to those with < median exposures, because all the kidney cancer deaths occurred in participants with ≥ median exposures. In contrast, Silver *et al*. (2014) reported a risk estimate of 0 comparing kidney cancer mortality in female salaried employees at a microelectronics facility to that in the US population because there were no exposed female kidney cancer deaths in this cohort.

Most studies reported several risk estimates. Most estimates were between 1 and 2 and not statistically significant. The studies that reported very strong risk estimates (*i.e*., >3) were based on a small number of exposed cases (*i.e*., mostly <10).

Five cohort studies evaluated kidney cancer risk based on concentrations or levels of exposure. One study reported no exposure-response relationship (*i.e*., p-trend >0.05) (Zhao *et al*., 2005), and three studies did not report p-trends (Morgan *et al*., 1998; Radican *et al*., 2008; Bove *et al*., 2014a). ATSDR (2018b) stated there was an exposure-response relationship, but did not evaluate statistical significance. Also, this study had no individual exposure data, a very high potential for selection bias, and a high correlation between chemical concentrations in the water so the results were not specific to TCE.

Six case-control studies evaluated levels of TCE exposure and kidney cancer risk. Two studies reported no exposure-response relationship (*i.e*., p-trend >0.05) (Michalek *et al*., 2019; Andrew *et al*., 2022), and two did not report a p-trend but reported that there were no statistically significant increased risks at any level of exposure (Vlaanderen *et al*., 2013; Pesch *et al*., 2000a). In all these studies, the interpretation of reported risk estimates is undermined by methodological study limitations, most notably a high likelihood of exposure measurement error, resulting in either inaccurate or biased effect estimates that are difficult to interpret.

While Andrew *et al*. (2022) found no trend, these authors evaluated kidney cancer risk associated with modeled concentrations of TCE in groundwater based on residential addresses, but modeled data were not linked to individual consumption data. Michalek *et al*. (2019) evaluated kidney cancer risk in Finland, Iceland, and Sweden using exposure data derived from the Nordic Occupational Cancer Study (NOCCA)-JEM in cases recruited from national cancer registries and controls recruited from the NOCCA cohort. The estimated exposure categories and associated risk estimates in Michalek *et al*. (2019) were low, <3,192.54 ppm-yr (OR = 1.00, 95% CI: 0.94-1.07); moderate, 3192.54-12,785.08 ppm-yr (OR = 0.92, 95% CI: 0.85-1.00); and high >12,785.08 ppm-yr (OR = 1.03, 95% CI: 0.88-1.19) (p-trend = 0.61). There is a high likelihood of exposure misclassification in this study because exposure estimates were based occupations reported on census surveys linked to an unvalidated JEM and because there was not much measurement data for the earliest time periods. The authors stated that these represented "worst case scenarios" and may have resulted in an overestimation of exposure.

The only two case-control studies to report a clear exposure-response relationship (*i.e*., p-trends <0.05 based on concentrations of exposure) were Charbotel *et al*. (2006) and Moore *et al*. (2010)/Purdue *et al*. (2021). US EPA (2011) concluded that Charbotel *et al*. (2006) and Moore *et al*. (2010) had the most reliable exposure estimates. The categorical mean cumulative exposures (and ranges) in Charbotel *et al*. (2006) were estimated to be 62.4 (1-150), 253.2 (155-335), and 925.0 (>335 – upper limit not reported) ppm-yr, respectively (as reported in US EPA, 2011). Charbotel *et al*. (2006) conducted analyses including all job periods and those "considering only job periods with a good level of confidence for TCE exposure assessment." Analyses with all job periods were used by US EPA (2011) in its human health risk assessment for TCE. Charbotel *et al*. (2006) reported ORs for low, medium, and high exposure as 1.62 (95% CI: 0.75-3.47), 1.15 (95% CI: 0.47–2.77), and 2.16 (95% CI: 1.02-4.60), respectively (p-trend = 0.04). However, the study had several limitations, including that controls were selected from urologist office

records, the reliance on self- or proxy-reported occupational histories, and the fact that it did not consider some important potential confounders like alcohol consumption and diabetes.

Moore *et al*. (2010) and Purdue *et al*. (2021) also reported an association between TCE exposure and kidney cancer, but at much lower exposure concentrations; median cumulative exposure levels were 1.58 ppm-years. These studies reported statistically significant dose-response relationships overall (p-trend ≤0.02) (Moore *et al*., 2010) and with the clear cell B RCC subtype (p-trend = 0.049) but not the clear cell A subtype (p-trend = 0.94) (Purdue *et al*., 2021). Moore *et al*. (2010) also reported an increased risk for RCC based on above-average hours exposed (OR = 2.22, 95% CI: 1.24-3.99, p-trend = 0.01) and increased exposure intensity (OR = 2.34, 95% CI: 1.05-5.21, p-trend = 0.02). These studies had similar limitations as Charbotel *et al*. (2006), in that controls were selected from hospital records, occupational histories were based on self-reports, and many important covariates (*e.g*., alcohol consumption and diabetes) were not considered. As noted in Section 6.1.1.2, US EPA (2011) also noted several issues with how cumulative exposures were estimated.

It is notable that Moore *et al.* (2010) and Purdue *et al*. (2021) reported similar risk estimates as Charbotel *et al*. (2006), though the estimated exposures in Charbotel *et al*. (2006) were much higher and are considered to be more reliable (US EPA, 2011).[9]

There are several studies that reported an association in populations that were considered to have high levels of exposure or high-probabilities of exposure at some point in time (*e.g*., Henschler *et al*., 1995a; Raaschou-Nielsen *et al*., 2003). These studies were of lower quality with respect to exposure characterization than Charbotel *et al*. (2006) but they provide some additional evidence, although limited, of an association between high occupational levels of TCE and kidney cancer.

I identified one pooled study and four meta-analyses that estimated associations between TCE and kidney cancer (Attachment D, Table D.5). The pooled analysis did not report any increase in kidney cancer risk overall, by sex, or with varying U-TCA levels, although U-TCA is not specific to TCE exposure (Hansen *et al*., 2013). All the meta-analyses reported an association between TCE and kidney cancer. Two studies conducted meta-analyses in a subset of studies that were determined to have higher quality exposure estimates (Wartenberg *et al*., 2000; Kelsh *et al*., 2010). Wartenberg *et al*. (2000) reported an increased risk of incident kidney cancer (SIR = 1.7, 95% CI: 1.1-2.7), but no increased risk of kidney cancer mortality (SMR = 1.2, 95% CI: 0.8-1.7). Kelsh *et al*. (2010) reported an increased risk of kidney cancer incidence and mortality combined (SRRE = 1.34, 95% CI: 1.07-1.67).

Two meta-analyses did not stratify by study quality (Scott and Jinot, 2011; Karami *et al.*, 2012a). Scott and Jinot (2011) reported an increased risk of kidney cancer in all studies (RRm = 1.27, 95% CI: 1.13-1.43) and in an analysis that evaluated risk in only the highest exposure group of included studies (RRm = 1.58, 95% CI: 1.28-1.96). These analyses were included in the US EPA (2011) evaluation of TCE (discussed in more detail in Section 6.4.3). Karami *et al*. (2012a) reported an association between TCE exposure and kidney cancer and RCC incidence (RR = 1.31, 95% CI: 1.01-1.69) but not mortality (RR = 1.16, 95% CI: 0.78-1.74).

All of the pooled and meta-analyses incorporated some of the cohort and case-control studies reviewed here and were limited by the underlying limitations of the analyzed studies, as described Section 6.1.1 and Attachment C, Table C.1. As these analyses were conducted several years ago, none included the more recent studies published in the last decade (*e.g*., Michalek *et al*., 2019). Most notably, pooling or averaging

[9] The categorical mean cumulative exposures in Charbotel *et al*. (2006) were estimated to be 62.4, 253.2, and 925.0 ppm × years, respectively, as reported in US EPA (2011) based on personal communication. Moore *et al*. (2010) reported cumulative exposure levels of <1.58 ppm × years and ≥1.58 ppm.

results across studies could not overcome the critical limitations of non-specific and indirect exposure characterization and uncontrolled and residual confounding.

6.1.3 Conclusions

Associations between TCE exposure and kidney cancer in epidemiology studies were mostly between 1 and 2, as confirmed in meta-analyses. The study with the most robust exposure estimates according to US EPA (2011) – Charbotel *et al*. (2006) – reported associations between very high TCE exposures (*e.g*., >335 ppm-yr) and kidney cancer, although, like other epidemiology studies, this study had several methodological limitations (*e.g*., inappropriate comparison groups, self-reported occupational histories, and residual confounding). Still, based on the consistency of risk estimates >1 and primarily Charbotel *et al*. (2006), I conclude that the epidemiology evidence provides support for associations between kidney cancer and very high occupational TCE exposures (*i.e.*, >335 ppm-yr).

6.2 Toxicology

6.2.1 Animal Carcinogenicity Studies

I identified 11 oral and nine inhalation chronic bioassays that stated they evaluated TCE exposure and the kidney. 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 11 chronic oral TCE bioassays in rats and mice, there were statistically significant increases in kidney tumor incidence in two NTP (1988, 1990) bioassays, but the study authors concluded that the findings were "inadequate" and "equivocal," respectively, due to reduced survival in treated animals, among other issues. Specifically, NTP (1988) reported a statistically significant increase in benign kidney tumors (renal tubular adenoma) in male Osborne-Mendel rats administered the middle, but not the highest, TCE dose. No significantly elevated kidney tumors were observed in female Osborne-Mendel rats, nor in three other strains of rats at any sex or dose (NTP, 1988). NTP (1988) did not conclude that the kidney tumors were caused by TCE, but instead concluded, "The studies are considered inadequate for either comparing or assessing trichloroethylene-induced carcinogenesis in these strains of rats." NTP (1988) noted that "the doses of trichloroethylene selected for the 2-year studies were too high," which reduced animal survival in each treatment group, "a large number of accidental deaths" in the high-dose group due to accidental gavage error, and "deficiencies in the conduct of the studies." Overall, this study does not provide evidence supporting TCE as a cause of kidney cancer in humans.

In a subsequent study, NTP (1990) reported statistically significantly elevated malignant tumor incidences (renal tubular adenocarcinoma) only in male F344/N rats administered the highest TCE dose. A few benign and malignant kidney tumors were observed in female F344/N rats and male B6C3F1 mice, but none were significantly elevated or due to treatment (NTP, 1990). In contrast to the previous study, NTP (1990) stated, "Under the conditions of these studies, epichlorohydrin-free trichloroethylene caused renal tubular cell neoplasms in male F344/N rats" based on their rarity in historical controls. However, NTP ultimately 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." US EPA (2011) acknowledged the high rates of death by gavage error in this study, but stated, "[H]istorical control incidences at NTP of kidney tumors in F344 rats is very low,

lending biological significance to their occurrence in this study, despite the study's limitations." US EPA's conclusion is not consistent with NTP's and does not fully consider that this study has major methodological limitations and equivocal results. This study alone does not provide adequate evidence to support a causal association between TCE and kidney cancer in humans. In the remaining studies, a few benign and malignant tumors were observed in rats and mice, but none were significantly elevated in any sex or species at any dose (NCI, 1976; Van Duuren *et al*., 1979; Maltoni *et al*., 1986, 1988a; Henschler *et al*., 1984).

I identified nine chronic inhalation TCE bioassays, none of which observed statistically significant increases in kidney tumors in any sex or species at any dose. Henschler *et al*. (1980) reported a few benign and malignant kidney tumors in rats, mice, and hamsters, but concluded they were not statistically significant or related to treatment. In addition, the exposure duration was insufficient in rats (78 weeks), and the observation period was inappropriate for both rats and mice (156 and 130 weeks, respectively). Fukuda *et al*. (1983) reported one clear cell carcinoma among 51 female rats at 450 parts per million (ppm), but, in this study, TCE contained the stabilizer compound epichlorohydrin, a known carcinogen, and animal husbandry was inadequate because "a few [animals] were killed accidentally, severely autolyzed or cannibalized, and died before the first appearance of tumors, reporting, and allocation." Finally, Maltoni *et al*. (1986, 1988a) reported a few malignant kidney tumors in Sprague-Dawley rats, but none were significantly elevated. Although not statistically significant, Maltoni *et al*. (1986, 1988a) concluded that the kidney tumors were caused by TCE exposure due to their rarity in historical controls. However, animals were observed until "spontaneous death" (Maltoni *et al*., 1986, 1988a), which could have resulted in late-life background pathology.

Collectively, chronic animal bioassays do not support a causal association between TCE exposure and kidney cancer in humans.

6.2.2 Mechanistic Studies

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, the liver and kidney have the highest concentrations of TCE metabolites due to local formation in these organs (IARC, 2014a). Although TCE does not cause kidney cancer in most animal studies, there is mechanistic evidence to support a potential mutagenic MoA for kidney cancer involving glutathione conjugation pathway metabolites.

While the major oxidative metabolites of TCE are not mutagenic in most studies, 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, 2020a; ATSDR, 2019a; 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, 2020a). 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, 2020a). 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, 2020a).

Various biological processes have been proposed to be involved in the MoAs for liver and kidney cancer as a result of TCE exposure, including oxidative stress, inflammation, gene expression changes, and immune-mediated effects (US EPA, 2020a; Zhu *et al*., 2024; Lash, 2024). Genetic polymorphisms in genes involved in the glutathione conjugation pathway and the inactivation of the tumor suppressor gene, von

Hippel-Lindau (*VHL*), have been suggested to potentially influence susceptibility to TCE-induced kidney cancer (US EPA, 2011, 2020a). 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, 2020a; ATSDR, 2019a). 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 are unknown.

Although there is uncertainty regarding the contribution of TCE genotoxicity to carcinogenicity in humans (US EPA, 2020a), 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 cancer types (ATSDR, 2019a; IARC, 2014a; US EPA, 2011, 2020a).

6.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated TCE and kidney cancer (see Section 6.1 and 6.2). Most of relevant epidemiology studies accounted for temporality, had higher-quality outcome assessments and study designs. Control for potential confounders varied across studies, but none sufficiently controlled for all important potential confounders. Several case-control studies had inappropriate control selection increasing the potential for selection bias. Most importantly, with the exception of Charbotel *et al*. (2006), none of the studies adequately assessed TCE exposures, calling into question the validity of reported risk estimates. Although limited in number, animal studies do not provide consistent evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence in the context of Bradford Hill's considerations, in Table 6.1. I conclude that the evidence provides support for an association between kidney cancer and very high occupational TCE exposures (*e.g.*, >335 ppm-yr in Charbotel *et al.*, 2006).

Table 6.1 Bradford Hill Assessment of TCE and Kidney Cancer

Aspect	Analysis
Strength of Association	There is evidence of a relatively strong association between high occupational TCE exposure (*e.g.*, >335 ppm-yr in Charbotel *et al.*, 2006) and kidney cancer risk. Most other risk estimates, including meta-analysis risk estimates, were between 1 and 2.
Consistency	Risk estimates varied, but most were consistently between 1 and 2 and not statistically significant.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between TCE and kidney cancer.
Temporality	Temporality was adequately addressed in most studies, but many studies did not consider an appropriate latency period and many case-control studies did not clearly define the exposure period.
Dose-Response	In the studies with the most robust exposure estimates and very high TCE exposures, there was a trend of increasing risk with increasing exposure (Charbotel *et al*., 2006; Moore *et al*., 2010).
Biological Plausibility	There is evidence to support a mutagenic MoA for TCE-induced kidney cancer *via* glutathione conjugation pathway metabolites, but it is unclear if this MoA occurs in humans.
Coherence	With the exception of two high-quality epidemiology studies, the observed associations in epidemiology studies are not sufficiently supported by strong, consistent, or compelling experimental evidence. Associations in epidemiology studies were generally above 1 but mostly weak, and study limitations, particularly with respect to exposure estimates, make the

Aspect	Analysis
	interpretation of most study results difficult. TCE caused slight increases in kidney tumors in male rats, but not female rats or mice or hamsters of either sex. Some evidence suggests that glutathione-conjugation metabolites may cause TCE-induced kidney tumors *via* a mutagenic MoA. However, these metabolites are formed by a minor metabolic pathway in humans relative to oxidative metabolism, and there is some uncertainty as to whether TCE metabolism in humans is sufficient to support this MoA for kidney cancer.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to TCE with respect to kidney 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 (2017) 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 conclude that the scientific evidence indicates that TCE can cause kidney cancer in humans (ATSDR, 2019a; IARC, 2014a; NTP, 2021a; US EPA, 2011, 2020a). 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.

ATSDR (2017a) determined there is sufficient evidence for causation for TCE and kidney cancer, based on "findings of increased risks of kidney cancer from exposures to TCE and the supporting mechanistic information" (ATSDR, 2017a). Regarding epidemiology evidence, ATSDR (2017a) placed the most weight on three meta-analyses with consistently elevated summary RRs in the 1.3-1.4 range (Scott and Jinot, 2011; Karami *et al*., 2012a; Kelsh *et al*., 2010) and the study by Moore *et al*. (2010). The meta-analyses found that higher cumulative exposures to TCE were associated with an increased risk of kidney cancer. ATSDR (2017a) stated that the findings of the study by Moore *et al*. (2010), which was considered to be of "high utility" by NTP (2015), were "in agreement with the hypothesized mechanism for TCE-induced kidney cancer and therefore provide strong evidence of causality." Regarding mechanistic evidence, ATSDR (2017) cited the conclusions by NTP (2015). ATSDR (2017a) briefly noted that TCE "has been observed to cause kidney cancer in rats" after exposure by inhalation or by stomach tube, but did not discuss any rat studies. ATSDR (2017a) also noted that there is support for "a mutagenic and cytotoxic mode of action mediated by GSH-conjugation-derived metabolites," as stated by NTP (2015).

In its Toxicological Profile for TCE, ATSDR (2019a) 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)…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." While ATSDR (2019a) did not state the studies on which it relied in deriving its conclusion, it cited the conclusions reached by NRC (2006) and the meta-analysis of 15 cohort and case-control studies conducted by US EPA (2011) reporting a significant association between overall TCE exposure and kidney cancer. ATSDR (2019a) noted that there is evidence for carcinogenic mechanisms involving mutation and cytotoxicity followed by regenerative proliferation due to the formation of reactive TCE metabolites, as discussed by US EPA (2011), but the evidence was primarily from studies of TCE metabolites rather than TCE. ATSDR (2019a) stated that these mechanisms are "considered biologically plausible, but without experimental support."

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 epidemiology studies (Henschler *et al*., 1995b; Vamvakas *et al*., 1998; Pesch *et al*., 2000a) that it judged were of insufficient quality for drawing conclusions due to small sample sizes, poor exposure data, a cluster study design, and/or unpersuasive results. IOM (2003) further elaborated, "Because of the small numbers of cases, most studies on exposure to trichloroethylene and kidney cancer lacked the power to detect excess risks." On this basis it concluded that there was "insufficient evidence to determine whether an association exists." IOM (2003) did not address animal or mechanistic evidence.

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) conducted an updated review with six additional cohort studies (Morgan and Cassady, 2002; Chang *et al*., 2003; Raaschou-Nielsen *et al*., 2003;

Zhao *et al.*, 2005; Boice *et al.*, 2006; Sung *et al.*, 2007) and two additional case-control studies (Brüning *et al.*, 2003; Charbotel *et al.*, 2006). NRC (2009) found that, while some of the more recent studies showed evidence of a dose-response relationship with kidney cancer (*i.e.*, Raaschou-Nielsen *et al.*, 2003; Zhao *et al.*, 2005), the studies often had small numbers of exposed participants and variable quality in exposure data and assessment methods. The agency noted that "[a] low incidence of kidney cancer is seen in male but not female rats in TCE…cancer bioassays," citing ATSDR (1997), and that humans are likely to be less susceptible than rats to TCE carcinogenicity due to lower absorption and less rapid metabolism to reactive metabolites.

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 kidney 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) also noted that rodents exposed to TCE have developed kidney cancer, citing NCI (1976) and NTP (1988, 1990), and discussed the metabolism of TCE to reactive species that may cause kidney damage, but did not draw any conclusions about the relevance of this pathway to human exposures.

6.4.3 US EPA

US EPA (2011) 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."

In this TCE review, US EPA (2011) identified 24 studies on TCE exposure and kidney cancer. US EPA (2011) placed the most weight on 15 cohort and case-control studies of what it considered to be sufficient quality, with most estimating RRs for kidney cancer between 1.1 and 1.9. Six of the studies reported statistically significant increased risks for overall TCE exposure (Moore *et al.*, 2010; Brüning *et al.*, 2003; Raaschou-Nielsen *et al.*, 2003; Dosemeci *et al.*, 1999) or in one of the highest TCE exposure groups (Moore *et al.*, 2010; Charbotel *et al.*, 2006; Zhao *et al.*, 2005; Raaschou-Nielsen *et al.*, 2003). In a meta-analysis of the overall effect of TCE exposure on kidney cancer, US EPA (2011) concluded that epidemiology studies suggested a "small, statistically significant increase in risk" of kidney cancer associated with TCE exposure based on 17 studies (meta-RR = 1.27, 95% CI: 1.28-1.96) (US EPA, 2011). US EPA (2011) noted that no individual study influenced the association. US EPA stated that the individual epidemiology studies along with the meta-analysis supported the consistency of the observed association, strength of the observed association, temporality, and the presence of a biological gradient (US EPA, 2011).

US EPA (2011) also discussed rodent bioassays in which male rats had increased incidences of kidney tumors that are rarely seen in historical controls, and considered these finding biologically significant even

though the evidence was limited by small increases that were only observed at high exposures (*e.g.*, 600 ppm in inhalation studies and 1,000 mg/kg-day in oral exposure studies), citing NTP (1988, 1990), Maltoni *et al*. (1986, 1988a), NCI (1976), Henschler *et al*. (1980), and Fukuda *et al*. (1983). US EPA (2011) acknowledged that the only two studies that reported statistically significant findings (NTP, 1988, 1990) were of low quality and do not provide adequate evidence to support a causal association between TCE and kidney cancer in humans. US EPA (2011) stated, "Several studies in rats were limited by excessive toxicity, accidental deaths, or deficiencies in reporting (NTP, 1990, 1988; NCI, 1976). Individually, therefore, these studies provide only suggestive evidence of renal carcinogenicity."

US EPA (2011) also concluded that the mechanistic evidence supports a mutagenic MoA mediated by reactive metabolites of TCE, and that cytotoxicity due to reactive metabolites leading to regenerative cell proliferation may also be a contributing MoA, but this has not been shown experimentally. US EPA (2011) described the potential role of the *VHL*[10] gene, stating, "Some, but not all, human studies have suggested a role for *VHL* mutations in TCE-induced kidney cancer (Charbotel *et al.*, 2007; 2004; Brauch *et al.*, 1999; Schraml *et al.*, 1999; Brüning *et al.*, 1997b)." US EPA (2011) noted that few animal studies have examined the role of TCE and *VHL* gene mutations, with Mally *et al*. (2006), which did not report *VHL* gene mutations in TCE-exposed Eker rats, being the only study mentioned to directly examine *VHL* mutations following exposure to TCE. US EPA (2011) concluded that "available data on the *VHL* gene in humans or transgenic animals do not conclusively elucidate the role of *VHL* mutation in TCE-induced renal carcinogenesis."

US EPA's most recent evaluation of TCE, published in November 2020, reaffirmed its previous conclusion that TCE is "carcinogenic in humans" based on "positive associations for NHL, kidney cancer and liver cancer with exposure to TCE" (US EPA, 2020a). US EPA (2020a) also noted that bioassays with TCE showed increased kidney tumors in male rats, but not female rats, mice, or hamsters, and cited "clear evidence" of a genotoxic MoA.

6.4.4 IARC

In 2014, IARC classified TCE as "carcinogenic to humans (Group 1)" based on "sufficient evidence" of kidney cancer in humans, and "sufficient evidence" of carcinogenicity in experimental animals (IARC, 2014a). With respect to kidney cancer, IARC reviewed several occupational cohorts, case-control studies, and meta-analyses and concluded, "Trichloroethylene causes cancer of the kidney" (IARC, 2014a). IARC (2014a) stated, "The majority of the Working Group concluded that the epidemiological data were sufficient; however a minority had concerns because most of the positive evidence came from case-control studies, while the data from cohort studies was weaker." IARC (2014a) gave the highest weight to the findings by Charbotel *et al*. (2009) and Moore *et al*. (2010), in addition to the meta-analyses by Scott and Jinot (2011) and Karami *et al*. (2012a).

IARC (2014a) also discussed "strong evidence" that TCE can be metabolized to reactive species that are genotoxic. Regarding the potential role of *VHL* mutations in the carcinogenic MoA for kidney cancer, IARC (2014a) cited Brüning *et al*. (1997), Brauch *et al*. (1999, 2004), Charbotel *et al*. (2007), and Moore *et al*. (2011), concluding, "The results regarding the association between renal cell carcinoma and mutations in the *VHL* gene were inconclusive." IARC (2014a) also cited the study by Mally *et al*. (2006), stating that the findings "were not associated with known, carcinogen-specific mutations in…the *VHL* gene." IARC (2014b) further elaborated, "Reported methodological difficulties and concern for bias in some studies prevented firm conclusions from being drawn."

[10] According to US EPA (2011), inactivation of the *VHL* gene through mutations, loss of heterozygosity, and imprinting has been observed in approximately 70% of RCC cases.

6.4.5 NTP

In the 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."

Regarding epidemiology evidence, NTP (2015) placed the highest weight on the studies by Charbotel *et al*. (2006, 2009), Moore *et al*. (2010), Zhao *et al*. (2005), Raaschou-Nielsen *et al*. (2003), and Brüning *et al*. (2003), in addition to the meta-analyses by Scott and Jinot (2011) and Karami *et al*. (2012a). NTP (2015) stated, "Toxicokinetic and mechanistic data in both humans and animals provide credible evidence for the biological plausibility of the proposed mechanisms of trichloroethylene's carcinogenicity in humans… [T]he mode of action for kidney carcinogenicity may involve a combination of mutagenicity and cytotoxicity" mediated by glutathione conjugation pathway metabolites. NTP (2015) noted that three studies (Brüning *et al*., 1997; Moore *et al*., 2010; Wiesenhutter *et al*., 2007) investigated GST polymorphisms and renal cell cancer among humans exposed to TCE, and provide support for the importance of the GSH conjugation pathway in renal cancer development. Of these studies, NTP (2015) described Moore *et al*. (2010) as the most informative. Regarding the potential role of *VHL* mutations in the carcinogenic MoA for kidney cancer, NTP (2015) cited the epidemiology studies by Brauch *et al*. (1999, 2004), Brüning *et al*. (1997), Charbotel *et al*. (2007), and Moore *et al*. (2011), and the animal study by Mally *et al*. (2006), concluding, "Further data are needed to determine the validity of *VHL* mutations as a legitimate biomarker for trichloroethylene-induced renal tumors" (NTP, 2015).

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 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. (NTP, 2021a)

Regarding human evidence for kidney cancer, NTP (2021a) placed the highest weight on the same studies as the NTP (2015) evaluation. 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, citing Maltoni *et al*. (1988a) and NTP (1988, 1990) bioassays for this conclusion.

6.4.6 Conclusions

Most government and scientific agencies conclude that the scientific evidence indicates that TCE can cause kidney cancer in humans (ATSDR, 2019a; IARC, 2014a; NTP, 2021a; US EPA, 2011, 2020a). All of these conclusions are based primarily on epidemiology evidence. Most agencies also noted a small increase in a type of kidney tumor in male rats exposed to high doses of TCE by inhalation or oral routes. This finding was considered to add support for the epidemiology findings based on the tumor's rarity in

historical controls, even though the investigators (NTP, 1990) concluded results were equivocal because dosed groups had reduced survival *vs*. vehicle controls. Most agencies also cited a likely MoA involving mutagenicity of reactive TCE metabolites (and possible regenerative cell proliferation), but NRC (2009) noted that "humans are likely to be less susceptible than rats to carcinogenicity from TCE due to lower absorption and less rapid metabolism to reactive metabolites."

6.5 Conclusions

Overall, government and scientific agencies conclude that there is evidence to support an association between TCE and kidney cancer in humans (ATSDR, 2019a; IARC, 2014a; NTP, 2021a; US EPA, 2011, 2020a). Some agencies noted that an association was supported by animal evidence, while acknowledging that this evidence was at most suggestive. Most agencies also cited a likely MoA in rodents involving mutagenicity of reactive TCE metabolites (and possible regenerative cell proliferation), but NRC (2009) noted that this MoA may be less relevant in humans because of differences in TCE absorption and metabolism between humans and rodents.

Regarding evidence from animal studies, a small increase in kidney tumors has been found only in male rats in a study that the investigators concluded was equivocal because dosed groups had reduced survival *vs*. vehicle controls. Kidney cancer was not increased in TCE-treated female rats, or in mice or hamsters of either sex in other studies. There is some evidence supporting a genotoxic MoA mediated by reactive metabolites of TCE; however, there is uncertainty regarding whether TCE metabolism in humans is sufficient to cause kidney cancer.

Most risk estimates reported for TCE exposure and kidney cancer in epidemiology studies were between 1 and 2, and most were not statistically significant. In all studies, various methodological limitations could have biased results (*e.g*., inappropriate comparison groups, indirect exposure assessments, and residual confounding). Although study limitations make the interpretation of study results difficult (particularly with respect to exposure estimates), based on the relative consistency of risk estimates >1, and the results of Charbotel *et al*. (2006) (which has the most robust exposure estimates according to US EPA, 2011), I conclude that the epidemiology evidence provides support for an association between kidney cancer and very high occupational TCE exposures (*e.g.*, >335 ppm-yr in Charbotel, *et al.*, 2006).

7 PCE and Kidney Cancer

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

7.1 Epidemiology

7.1.1 Overview

I identified 24 cohort studies (in 15 unique populations) and 16 case-control studies that evaluated PCE and kidney cancer. The majority of these studies were conducted in Europe and North America; the rest were conducted in Australia, New Zealand, and Taiwan. I review here all Camp Lejeune studies in which PCE exposures were specified, even if populations overlapped, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I describe 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 Attachments F and C, Tables F.1, F.3 and C.1, respectively. Study results are discussed briefly in Section 7.1.2 and reviewed in more detail in Attachment F, Tables F.2 and F.4. 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 kidney cancer were also drawn from appropriate populations in most case-control studies. A few case-control studies selected controls from populations that were not representative of the population from which the cases were drawn, and these studies 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 provided information, most had low rates of loss to follow-up (<20%). Most of the case-control studies reported low (<80%) or unknown participation rates in cases and/or controls, which may have resulted in selection bias. In only a few case-control studies did the participation rates between cases and controls differ by >15% (*e.g.*, in Purdue *et al.* [2017], 77% of eligible cases participated, compared to only 54% of eligible controls). 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 (2018b) 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 in all the cohort and case-control studies was the manner by which exposures were estimated. The epidemiology studies examining PCE exposure and kidney cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, launderers and dry cleaners). All the 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). The reliance on occupations and job titles as surrogates for exposure, even when coupled with semi-quantitative measures of exposure, does not provide information on individual exposure levels. No studies used directly measured air or water exposure concentrations at the individual level to estimate exposure concentrations, however, Anttila *et al*. (1995) used U-TCA and blood PCE levels from an occupational monitoring program to identify ever exposed participants when designing their study.

Bove *et al*. (2014a,b) and ATSDR (2018b) 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). None 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 (2018b), 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 after kidney cancer had been diagnosed (*e.g.*, Asal *et al*., 1988). 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, which occurs when cases 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 exposure conditions did so based on modeled contamination in drinking water (with no individual consumption/exposure data), a JEM, or duration of employment; these measurements are at best crude estimates of actual exposures with an unknown amount of error. In addition, most 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

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 case ascertainment, namely when relying on self-report without another source of identification (such as a registry to identify cases who did not self-report or who were deceased, *e.g.*, ATSDR, 2018b). 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. Case-control studies generally controlled for a larger number of important covariates than the cohort studies. Most cohort studies controlled for age and sex, while other variables were controlled for less consistently (*e.g.*, race, smoking, and obesity). Only Karami *et al.* (2012b) controlled

for a family history of cancer; no studies controlled for genetic factors or diabetes. 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 or diabetes status). Most of the studies did not provide information on the degree or impact of missing covariate data.

7.1.1.5 Temporality

Most cohort studies assessed or considered exposures occurring prior to the outcome, but many did not ensure an appropriate duration of time was considered between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥4 years for kidney 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. Most of the case-control studies collected information on exposures after diagnosis, increasing the potential for recall bias. Most case-control studies did not report the exposure period, making it difficult to determine if an appropriate latency period was considered.

7.1.2 Study Results

Cohort and case-control studies reported a wide range of risk estimates for PCE and kidney cancer incidence (range: 0.24-41.54) and mortality (range: 0.15-24.4), with two exceptions (Bove *et al*., 2014b; Silver *et al*., 2014). Bove *et al*. (2014b) reported an HR = ∞ comparing kidney cancer mortality in Camp Lejeune civilian employees with ≥ median cumulative PCE exposures compared to those with < median exposures, because all the kidney cancer deaths occurred in the higher exposure category. In contrast, Silver *et al*. (2014) reported a risk estimate of 0 comparing kidney cancer mortality in female salaried employees at a microelectronics facility to that in the US population because there were no exposed female kidney cancer deaths in this cohort. Most risk estimates were not statistically significant (*i.e.*, only three out of 16 cohort studies – including three overlapping Camp Lejeune populations – and six of 16 case-control studies reported some statistically significant estimates). Most of the risk estiamtes that were high in magnitude, including those that were statistically significant, were based on a small number of cases and had wide CIs, indicating they were statistically unstable, and many were reported based on indirect exposure estimates (*e.g.*, from job titles or work histories), so the reported risks cannot be attributed to PCE.

Of the 16 studies that examined at least three levels of exposure, most reported similar risk estimates across all levels of exposure. Five studies reported at least one statistically significant estimate based on duration, intensity, and/or frequency (ATSDR, 2018b; Callahan *et al*., 2019; Pesch *et al*., 2000a; Purdue *et al*., 2017). Pesch *et al*. (2000a) reported mixed results in their analyses (*e.g.*, based on sex and job-exposure matrix approaches); when using a German JEM the authors observed a statistically significant increase in kidney cancer incidence for males based on medium exposure levels (OR = 1.4, 95% CI: 1.1-1.7) but did not observe any association based on higher exposure levels in males, or any exposures in females, or when using a JTEM approach. Purdue *et al*. (2017) also reported mixed results in most of their analyses (*e.g.*, based on PCE exposure probability or total years exposed), but they observed a statistically significant elevated risk based on the highest tertile of cumulative hours exposed (>1,820 hours) among those employees with high-intensity exposure (OR = 3.1, 95% CI: 1.3-7.4). Callahan *et al*. (2019) reported some associations based on 10-year (HR = 17.8, 95% CI: 2.2-143.7, p-trend = 0.004) and 20-year lags (HR = 24.4, 95% CI: 2.9-201.6, p-trend = 0.0004) for subjects with high intensity solvent exposures in the dry-cleaning industry when compared to those with no or low intensity solvent exposure. These estimates are based on just three cases resulting in very wide CIs, and exposures were not specific to PCE (*i.e.*, estimated solvent exposures based on a JEM).

ATSDR (2018b) reported a statistically significant elevated risk for kidney cancer incidence among Camp Lejeune Marines and Navy personnel with medium (OR = 1.43, 95% CI: 1.02-2.00) and high cumulative

exposure to PCE (OR = 2.01, 95% CI: 1.29-3.13) when compared to those with low exposure. Similarly, there was a statistically significant elevated risk among civilian employees with medium exposure (OR = 5.34, 95% CI: 1.38-20.6) to either TCE and PCE, when compared with civilian employees with low exposures. According to the authors, TCE and PCE exposures for civilians were perfectly correlated, so these results cannot be attributed to PCE specifically.

All other studies using semiquantitative exposure measurements reported null results that were both above and below 1, but mostly above 1. Some studies reported increasing risk with increasing exposure, but most observed either higher risks in lower-exposure groups and not in the higher-exposure groups (*e.g.*, Lipworth *et al.*, 2011), or a similar magnitude of risk across all exposure groups (*e.g.*, Bove *et al.*, 2014a). Most of the exposure-response estimates reported across studies were statistically null. Importantly, the interpretation of all reported risk estimates is undermined by methodological study limitations, most notably a high likelihood of exposure measurement error, resulting in either inaccurate or biased effect estimates that are difficult to interpret.

7.1.3 Conclusions

Most cohort and case-control studies did not find that PCE exposure was associated with kidney cancer or demonstrate exposure-response relationships. The studies reported a wide range of risk estimates, but most that were high in magnitude had wide CIs. All of the 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 important covariates (*e.g.*, smoking). I conclude that the epidemiology evidence does not support a causal association between PCE exposure and kidney cancer.

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 kidney. 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). While there were no reported treatment-related kidney tumors, the authors noted that, "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 [PCE]."

I identified four chronic inhalation PCE bioassays in two studies. Kidney tumors were not statistically significantly elevated in any sex or species at any dose in the mouse and rat bioassays. NTP (1986a) dosed F344/N rats and B6C3F$_1$ mice and found no benign or malignant tumors in female rats and mice, and only one malignant tumor in male mice. A small number of benign and malignant tumors were reported in male rats but, despite the lack of statistical significance, NTP (1986a) concluded these kidney tumors (primarily benign adenomas) were caused by PCE exposure due to the rarity of this tumor type in historical controls. However, there were early deaths in the male rats and mice and female mice, likely due to mononuclear cell leukemia or hepatocellular carcinomas that may have biased results, and there were two benign tumors in control male rats (NTP, 1986a). JISA (1993) reported a few benign and malignant tumors in male and female rats and male mice, but none reached statistical significance. No tumors were reported for female mice.

Collectively, chronic animal bioassays do not support a causal association between PCE exposure and kidney cancer in humans.

7.2.2 Mechanistic Studies

Epidemiology and animal evidence does not support PCE as a cause of kidney cancer, and there is insufficient evidence to establish a definitive MoA for PCE. Animal and human studies indicate that PCE metabolism is relatively limited, particularly at higher exposures (US EPA, 2012, 2020b), 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, 2020b; IARC, 2014b; Cichocki *et al*., 2016). Some PCE metabolites can enter systemic circulation and have been detected in urine; however, 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. 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, 2020b; 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, 2020b; 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 were observed). Whether oxidative stress and immune system alterations are involved in carcinogenicity induced by PCE is unknown (ATSDR 2019b; US EPA, 2020b).

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 (ATSDR, 2019b; IARC, 2014b; US EPA, 2012, 2020b).

7.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated PCE and kidney cancer (see Section 7.1 and 7.2). Most of the cohort and case-control studies had higher-quality study designs and outcome assessments and had low likelihoods of selection bias. The consideration of temporality and control for potential confounders varied across studies, but no study sufficiently controlled for all important potential confounders. Most importantly, none of the studies directly assessed individual PCE exposures, calling into question the validity of reported risk estimates. Although limited in number, animal studies do not provide evidence for causation. Keeping these study strengths and weaknesses in mind, I evaluated the available evidence 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 exposure and kidney cancer.

Table 7.1 Bradford Hill Assessment of PCE and Kidney Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between PCE exposure and kidney cancer in cohort and case-control studies.

Aspect	Analysis
Consistency	Risk estimates for PCE and kidney cancer were inconsistent; ranging widely within and between studies.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between PCE and kidney cancer.
Temporality	Temporality was not adequately addressed in most cohort and case-control studies, as many did not ensure an appropriate latency period between exposure and diagnosis (*i.e.*, ≥0.5 years).
Dose-Response	There were no consistent dose-response trends reported within or across studies.
Biological Plausibility	There is some evidence to support a potential mutagenic MoA for PCE-induced kidney cancer.
Coherence	Collectively, the evidence does not support a causal association between PCE exposure and kidney cancer. A wide range of risk estimates were reported across epidemiology studies, but the majority were statistically null, there were no consistent dose-response relationships within or across studies, and each epidemiology study had several methodological limitations that impacted the interpretation of its results. No chronic animal study has reported statistically significant increase of kidney tumors associated with oral (NCI, 1977) or inhalation exposure to PCE (NTP, 1986a; JISA, 1993). Although PCE metabolites may be mutagenic, evidence is insufficient to establish a definitive MoA for kidney cancer.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to PCE with respect to kidney 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 (2017) 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.

Government and scientific agencies conclude that the scientific evidence does not support a likely association between PCE and kidney cancer in humans (ATSDR, 2017a, 2019b; IOM, 2003, 2015; NRC, 2009; US EPA, 2012, 2020b; IARC, 2014b). 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) noted an increased incidence of kidney tumors in male rats exposed to PCE by inhalation in one bioassay by NTP (1986a). The agency concluded that the evidence for causation for kidney cancer was "below equipoise" (*i.e.*, below 50% likelihood) "due to the lack of consistency in the findings from the epidemiological studies" (ATSDR, 2017a).

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." While this document listed epidemiology studies that assessed the association between PCE exposure and kidney cancer, and described the NTP study that found increased kidney tumors in PCE-exposed rats, it did not state any conclusions regarding PCE and kidney cancer.

7.4.2 NASEM

Subcommittees of NASEM reviewed the associations between solvent exposures and kidney cancer in the contexts of the Gulf War and Camp Lejeune. Most of the epidemiology studies included in NASEM's reviews were not specific to PCE.

In 2003, IOM (2003) did not conclude that PCE was associated with any cancer type in humans. IOM determined that three studies (Mandel *et al*., 1995; McCredie and Stewart, 1993; Pesch *et al*., 2000a) provided limited/suggestive evidence of an association between exposure to PCE and dry-cleaning solvents and kidney cancer. NASEM defines "limited/suggestive evidence of an association" as "[e]vidence from available studies [that] suggests an association between exposure to a specific chemical and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence" (IOM, 2003).

In the assessment of potential health effects at Camp Lejeune, NRC (2009) identified five additional studies of PCE exposure and kidney cancer: three cohort studies (Morgan and Cassady, 2002; Blair *et al*., 2003; Chang *et al*., 2003) and two case-control studies (Brüning *et al*., 2003; Lynge *et al*., 2006). While NRC (2009) found that the PCE studies "largely showed no increase in risk," it nevertheless concluded that "there is limited/suggestive evidence of an association between chronic exposure to TCE or PCE and kidney cancer" (NRC, 2009).

NRC (2009) also discussed the findings in male rats exposed to PCE by inhalation, and noted that the tumors only occurred at high doses. NRC (2009) did not discuss likely mechanisms of PCE-induced kidney cancer in these rats.

In its 2015 review, an IOM committee identified additional studies of PCE exposure and kidney cancer that had been published since the NRC (2009) report (Christensen *et al*., 2013; Lipworth *et al*., 2011) and stated, "These new studies have generally supported the conclusions of the previous report" (IOM, 2015).

7.4.3 US EPA

US EPA (2012) concluded that PCE is "'Likely to be Carcinogenic to Humans' by all routes of exposure." US EPA (2012) stated, "This characterization is based on suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence (JISA, 1993; NTP, 1986a; NCI, 1977)." With regard to kidney cancer, US EPA (2012) stated that "[t]he epidemiologic data provide limited evidence pertaining to tetrachloroethylene exposure and kidney cancer risk" and that the limited data were "suggestive of an effect." The agency cited the study by Mandel *et al.* (1995) as the largest international case-control study that provides evidence in support of an association, in addition to three large cohort studies with mixed results (Pukkala *et al*., 2009; Travier *et al*., 2002; Ji *et al*., 2005), and eight additional cohort and case-control studies, with relatively specific exposure-assessment methodologies, that also had mixed results (Lynge *et al*., 2006; Pesch *et al*., 2000a; Boice *et al*., 1999; Dosemeci *et al*., 1999; Aschengrau *et al*., 1993; Calvert *et al*., 2011; Blair *et al*., 2003; Anttila *et al*., 1995; Schlehofer *et al*., 1995).

US EPA (2012) also noted that renal tubule tumors in male rats exposed to PCE by inhalation provided "convincing evidence of a treatment-related effect," because the spontaneous incidence of these tumors in rats is very low. US EPA (2012) described the mechanism believed to be responsible for the rat kidney tumors as likely mediated by reactive metabolites, and may "include mutagenicity, peroxisome proliferation, α2u-globulin nephropathy, and cytotoxicity not associated with α2u-globulin accumulation."

US EPA (2020b) 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 (2020b) 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 (2020b) 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 (2020b) included several additional epidemiology studies of kidney cancer (Bove *et al*., 2014a; Christensen *et al*., 2013; Lipworth *et al*., 2011; Purdue *et al*., 2017; Seldén and Ahlborg Jr., 2011; Siemiatycki, 1991; Silver *et al*., 2014; Vlaanderen *et al*., 2013). US EPA (2020b) concluded that "[s]tudies provide…little or no support for associations with kidney, esophagus, or liver cancer." Regarding kidney cancer specifically, US EPA (2020b) concluded that the findings "are consistent with no association or weak positive association between the occurrence of kidney cancer and exposure to PCE, but should be

interpreted with caution due to the small number of informative studies." This is consistent with US EPA's descriptor, "Inadequate Information to Assess Carcinogenic Potential" (US EPA, 2005).

US EPA (2020b) reiterated its conclusion that the renal tubule tumors in male rats exposed to PCE by inhalation were notable, and that the rarity of these tumors in control rats suggests "that these findings are biologically significant." Regarding a possible carcinogenic MoA, US EPA (2020b) stated that "available data provide evidence for mutagenicity as a potential MoA for renal carcinogenicity induced by PCE, however, there was not enough evidence to establish a definitive MoA for kidney 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 kidney cancer, IARC (2014b) reviewed several cohort, case-control, and ecological studies of PCE and kidney cancer and concluded, "No consistent patterns were seen across studies…some case-control studies were suggestive of a positive association for occupations involving exposure to tetrachloroethylene. However, the cohort studies generally did not find an association between tetrachloroethylene exposure and cancer of the kidney, and most studies did not evaluate or failed to show positive exposure- or duration-response relationships."

Regarding animal evidence, IARC (2014b) noted that "[t]here is some evidence that tetrachloroethylene is carcinogenic in the kidney in male rats" based on increased incidence of kidney tumors after exposure to 200 or 400 ppm PCE, but not in female rats or in mice, in one bioassay (NTP, 1986a). IARC noted that two other bioassays did not find kidney tumors in PCE-exposed rats or mice of either sex (NCI, 1977; JISA, 1993).

IARC (2014b) also concluded that the most likely mechanism of carcinogenesis in the kidney is genotoxicity generated by the formation of reactive PCE metabolites in the kidney but did not consider evidence of kidney tissue hyperplasia and other kidney tissue damage in male rats (NTP, 1986a) to be as relevant.

7.4.5 NTP

In the 2016 Report on Carcinogens Monograph on Tetrachloroethylene, NTP (2016) concluded that PCE is "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals." NTP (2016) stated that PCE caused liver tumors in mice, mononuclear cell leukemia (MNCL) in rats, and increased the incidence of benign and malignant kidney tumors in rats.

NTP (2016) did not discuss any epidemiology evidence, but noted that IARC (1995) 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." NTP (2016) further stated that "confounding by exposure to other chemicals could not be ruled out, and the total numbers in the combined cohort studies were small." NTP (2016) did not discuss IARC (2014), which came to different conclusions.

In its most recent evaluation of PCE, NTP (2021b) upheld its previous classification of PCE as "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals." NTP (2021b) cited the same experimental animal and epidemiology evidence as it did in 2016 to support this PCE cancer classification.

7.4.6 Conclusions

No agency has found consistent evidence of an association between PCE and kidney cancer in epidemiology studies, and none ruled out chance, bias, or confounding as a potential explanation for any observed associations. Most noted a small increase in kidney tumors in male rats exposed to high doses of PCE by inhalation. US EPA and IARC concluded the MoA was likely genotoxicity *via* a reactive PCE metabolite, although US EPA noted evidence was lacking "to establish a definitive MoA for kidney cancer." Some agencies noted there was no evidence for PCE-induced kidney cancer in female rats or mice. No agency concluded that there is more than limited or suggestive evidence that PCE can cause kidney cancer in humans, and none classified PCE as a known human carcinogen (ATSDR, 2017a, 2019b; IARC, 2014b; IOM, 2003, 2015; NRC, 2009; US EPA, 2012, 2020b; NTP, 2021b).

7.5 Conclusions

Government and scientific agencies conclude that the scientific evidence does not support a likely association between PCE and kidney cancer in humans (ATSDR, 2017a, 2019b; IOM, 2003, 2015; NRC, 2009; US EPA, 2012, 2020b; IARC, 2014b). The majority of the associations between PCE and kidney cancer in epidemiology studies were null and 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 their results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). Regarding experimental evidence, no chronic animal study has reported statistically significant increase of kidney tumors associated with or inhalation exposure to PCE. There is no MoA for kidney cancer with sufficient scientific support.

Because (1) the epidemiology studies are not of high quality and most analyses do not support 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 scientific evidence does not support a causal association between PCE and kidney cancer.

8 Benzene and Kidney Cancer

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

8.1 Epidemiology

8.1.1 Overview

I identified 48 cohort studies (in 25 unique populations) and six case-control studies (all conducted in unique populations), and one meta-analysis that evaluated benzene exposure and kidney cancer. Most of these studies were conducted in North America or Europe, two studies were conducted in Australia, and one study in Russia. 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 and quality, below and in Attachment H, Tables H.1, H.3, and Attachment C, Table C.1. Study results are discussed in Section 8.1.2 and in Attachment H, 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. However, most case-control studies did not draw controls from appropriate populations (*i.e.*, hospital-based or non-compulsory electoral roll-based controls). Most cohort studies did not report either rates of exclusion or loss to follow-up, and case-control studies either did not report or reported low participation rates, which increased the potential for selection bias. In the 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 (2018b) 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 exposures in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all cohort and case-control studies was the manner by which exposures were estimated. The epidemiology studies examining benzene exposure and kidney cancer were largely conducted among populations that represented specific occupational groups (*e.g.*, oil refinery and petroleum distribution workers). All studies estimated benzene exposure in an indirect manner, based on job title 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 concentrations evaluated at the individual level in any studies. Bove *et al*. (2014a,b) and ATSDR, 2018b) 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, none of these studies had individual-level water consumption/exposure data, so individual exposures were likely misclassified. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014a,b) and ATSDR (2018b), which limits the interpretation of the benzene-specific results.

All the case-control studies, except Greenland *et al.* (1994) characterized exposure based on self-reported work histories collected after kidney cancer had been diagnosed. 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 can occur when cases recall exposures differently than controls.

Many studies considered duration of exposure; however, very few considered the frequency or intensity of potential exposures. The studies that did attempt to account for frequency or intensity of exposure did so based on a JEM, duration of employment, or modeled drinking water contamination (with no individual consumption data); these measurements are at best crude estimates of actual exposures with an unknown amount of error. In addition, no study, except for Wong *et al*. (1993) and three of the Camp Lejeune studies (Bove *et al*., 2014a,b; ATSDR, 2018b), considered the time-varying nature of potential exposures (*i.e*., 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

Kidney cancer outcomes were obtained or confirmed using reliable and complete methods in most cohort and case-control studies. For example, the cohort studies identified or confirmed cases using medical records, registries, or government databases (*e.g*., national death index), and cases were medically confirmed in all case-control studies except for Greenland *et al*. (1994), in which 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 without another source of identification (such as a registry to identify cases who did not self-report or who were deceased [*e.g*., ATSDR, 2018b]). Most of the studies reported on kidney cancer or renal cell carcinoma incidence or mortality specifically. One study also reported on renal pelvic cancer (McCredie and Stewart, 1993).

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, and most controlled for race or ethnicity, but other variables were controlled for less consistently (*e.g*., smoking, alcohol consumption, other potential chemical exposures). None of the studies considered or controlled for hypertension, genetic factors, family history of kidney cancer, or diabetes. Even when important covariate data were collected, none of the studies accounted for the time-varying nature of some 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 assessed or considered exposures prior to the outcome, but many did not ensure an appropriate period of time was considered, either in the design or the analysis (*i.e.*, ≥4 years for kidney cancer). 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. Only one of the six case-control studies appropriately considered the latency period (Brüning *et al.*, 2003).

8.1.2 Study Results

Cohort and case-control studies reported a wide range of risk estimates for benzene and kidney cancer incidence (range: 0.38-3.13) and mortality (range: 0-4.4), but almost all were statistically null and most estimates were close to 1 (*i.e.*, in the majority of studies, almost all risk estimates ranged from 0.67 to 1.5). Among 47 cohort studies (in 25 unique populations) and six case-control studies, only eight cohort and two case-control studies reported statistically significant results, all but one of these estimates were above 1. Most of these statistically significant estimates were based on a small number of cases and had wide CIs, indicating they were statistically unstable, and many were reported based on indirect exposure estimates (*e.g.*, from job titles or work histories), so the reported risks cannot be attributed to benzene.

Of the 17 studies that examined at least three levels of exposure, most reported similar risk estimates across all levels of exposure. Only two studies reported statistically significant estimates based on duration, intensity, and/or frequency (Sorahan *et al.*, 2002; ATSDR, 2018b). Rushton *et al.* (1993) observed an elevated risk for kidney cancer mortality among oil refinery and petroleum distribution workers based on 30 to 39 years since first exposure (SMR = 1.80, 95% CI: 1.10-2.79), but risks decreased and became non-significant for longer durations, and "exposure" was based only on employment records and was not specific to benzene. ATSDR (2018b) reported a statistically significant elevated risk for kidney cancer incidence among Camp Lejeune Marines and Navy personnel with medium cumulative exposure to TCE, which was considered a surrogate for benzene (OR = 1.45, 95% CI: 1.05-2.00), but this association was not statistically significant for those with high TCE exposure (OR = 1.55, 95% CI: 0.95-2.54). These results were not specific to benzene exposure, however, as TCE, vinyl chloride, and total VOC concentrations were nearly perfectly correlated with benzene concentrations. All other studies using semiquantitative exposure measurements reported null results that were both above and below 1.

Six studies that evaluated benzene exposures or occupations associated with benzene exposure and kidney cancer risk were discussed by Plaintiffs' experts and were published before the start date of my literature search (Attachment A) but were not included in the agency reports I reviewed. I also identified one study (Demoulin *et al.*, 2024) that evaluated benzene exposures and kidney cancer risk and that was discussed by Plaintiffs' experts and published after I completed my literature search. I briefly describe these studies below.

Two of these studies evaluated kidney cancer risks based on employment in shoe factory manufacturing (Fu *et al.*, 1996; Walker *et al.*, 1993). Neither evaluated any chemical specific exposure, and neither reported any association between employment in the shoe industry and kidney cancer. Szeszenia-Dabrowska *et al.* (1991) examined kidney cancer risk among male employees at a rubber factory in Poland. They reported expected rates of kidney and other urinary organ cancers based on rates in the general male Polish population (SMR = 1.3, p-value >0.05). Hu *et al.* (2002) evaluated incident kidney cancer cases between 1994-1997 in Canada. They evaluated exposure to benzene using questionnaires on job history. They reported an increased risk of kidney cancer in men associated with any exposure to benzene (OR = 1.8, 95% CI: 1.2-2.6). They also reported an increased risk of kidney cancer associated with benzene exposures ≥6 years (OR = 2.1, 95% CI: 1.3-3.2) but not with shorter durations of exposure. Two studies

evaluated exposures to benzene *via* oil and gas. Seldén *et al*. (1991) reported expected rates of kidney cancer deaths in men in the Swedish armed forces exposed to aircraft fuel based on rates in the Swedish general population (SIR = 1.03, 95% CI: 0.21-3.01). Anttila *et al*. (2015) evaluated kidney cancer risk in Finnish oil refinery employees and based benzene exposure estimates on occupational hygiene assessments of personnel and pension files. They reported no associations with any duration of exposure (OR range: 1.37-2.98, p-trend = 0.062), mean annual level of exposure (OR range: 1.56-2.69, p-trend = 0.26), or level of cumulative exposure (OR range: 1.69-2.56, p-trend = 0.069).

Demoulin *et al*. (2024) evaluated kidney cancer risk in the population-based Shanghai Men's Health Study (SMHS) and the Shanghai Women's Health Study (SWHS) and estimated benzene exposures using JEMs. They reported no increased risk of kidney cancer associated with any level of cumulative benzene exposure in either cohort and reported no dose-response trends.

Like most of the epidemiology studies I reviewed, all of these studies have major methodological limitations, including the potential for exposure misclassification and residual and uncontrolled confounding.

8.1.3 Conclusions

Most cohort and case-control studies did not report associations between benzene exposure and kidney cancer or demonstrate exposure-response relationships. All cohort and case-control studies had critical methodological limitations that impact the validity of their results. The most critical limitation in all these studies was the high likelihood of exposure misclassification, resulting in either inaccurate or biased risk estimates that are difficult to interpret.[11]

8.2 Toxicology

8.2.1 Animal Carcinogenicity Studies

Seven chronic benzene oral bioassays evaluated the kidney. The results of these studies are reported in Attachment I, Table I.1. I identified eight chronic benzene inhalation bioassays. The results of these studies are reported in Attachment I, Table I.2. Maltoni *et al*. (1982, 1983, 1985, 1989) and Maltoni and Scarnato (1979) reported only one kidney tumor in 65 high-dose female rats (the authors did not evaluate multiple doses in males), but the authors examined animals following "spontaneous death" rather than at terminal sacrifice. In a good laboratory practice (GLP)[12] study, Huff *et al*. (1989)/NTP (1986b) reported one tubular cell adenocarcinoma in control male rats and one in mid-dose female mice, and one tubular cell adenoma in mid-dose male mice and none in high-dose groups. Neither of these studies provided evidence that benzene can cause kidney cancer. 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.

[11] The results of studies I identified from Plaintiffs' expert reports that were not included in the agency reports I reviewed or that were published after the completion of my literature search (Section 8.1.2) do not change my conclusions regarding benzene exposure and kidney cancer risk.

[12] OECD defines a GLP as "a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported" (OECD, 1998).

8.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which benzene could cause kidney 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, 2024a; 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 Myelodysplastic Syndrome [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, 2024a; US EPA, 1998; North *et al*., 2020). Reactive metabolites generated in the liver can also be transported to the bone marrow (ATSDR, 2024a).

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 kidney cancer, is unknown.

8.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated benzene exposure and kidney cancer (see Section 8.1 and 8.2). Most epidemiology studies had higher-quality study designs and outcome assessments and had low likelihoods of selection bias. The consideration of temporality, latency period, and control for potential confounders varied across studies, and none sufficiently controlled for all important potential confounders. Most importantly, none of the epidemiology studies adequately assessed benzene exposures using direct exposure measurements, calling into question the validity of reported risk estimates. Notably, while Bove *et al*. (2014a) reported benzene-specific risk estimates in their Camp Lejeune study, ATSDR (2018b) reported only risk estimates for TCE because categorical benzene exposures were correlated with categorical TCE, vinyl chloride, and TVOCs exposures (γ = 0.99). None of these exposure metrics accurately reflect individual exposures. Although limited in number and quality, animal studies do not provide evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence 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 exposure and kidney cancer.

Table 8.1 Bradford Hill Assessment of Benzene and Kidney Cancer

Aspect	Analysis
Strength of Association	There is no consistent evidence of a strong association between benzene exposure and kidney cancer in cohort and case-control studies.
Consistency	Risk estimates for benzene and kidney cancer were not consistently elevated.

Aspect	Analysis
Specificity	There is no currently available evidence to suggest that there is a specific relationship between benzene and Kidney cancer.
Temporality	Temporality was adequately addressed in most cohort and case-control studies; however, most studies did not consider an appropriate latency period and some case-control studies did not clearly define the exposure period.
Dose-Response	There were no consistent trends of increasing risk with increasing exposures across studies that considered multiple exposure levels.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which benzene could cause kidney cancer.
Coherence	Collectively, the evidence does not support a causal association between benzene exposure and kidney cancer. The majority of the associations between benzene and kidney cancer in epidemiology studies were close to 1 and statistically null, there were no consistent dose-response relationships across studies, and all epidemiology studies had methodological limitations that impacted the interpretation of results. Although there is evidence that reactive metabolites of benzene may cause certain cancers *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 this MoA is applicable to kidney cancer or that benzene causes kidney cancer in animal models.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compound to benzene that cause kidney cancer.

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; 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 (2017) 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.

Government and scientific agencies conclude that there is no evidence to support an association between benzene and kidney cancer in humans (ATSDR, 2007a, 2015, 2017a; US EPA, 1998; IARC, 2018; IOM, 2003, 2015; NRC, 2009). These 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). ATSDR did not discuss kidney cancer in either the 2007 Benzene Toxicological Profile (ATSDR, 2007a) or in the 2015 Supplemental Report (ATSDR, 2015). In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) did not discuss or draw any conclusions regarding benzene and kidney cancer. In 2024, ATSDR released a Draft Toxicological Profile for Benzene for Public Comment. Kidney cancer is not discussed in this report (ATSDR, 2024a).

8.4.2 NASEM

IOM (2003) noted one case-control study that did not show an association between benzene and kidney cancer (Gérin *et al*., 1998). 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 kidney cancer in relation to benzene.

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 kidney cancer in its review of the carcinogenic effects of benzene (US EPA, 1998).

8.4.4 IARC

IARC (2012a) concluded that, "There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia." For kidney cancer, IARC (2012a) stated that, "Results generally do not show any association" and did not make a casual determination.

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."

IARC (2018) identified one cohort (Bove *et al*., 2014a) and two case-control studies (Pesch *et al*., 2000a; Gérin *et al*., 1998) of benzene and kidney cancer, and did not conclude that there was sufficient evidence of an association. Regarding the evidence for kidney cancer, along with some other cancers, IARC (2018) stated, "Each of these cancers was addressed in a small number of studies. For each cancer site, results were inconsistent across studies, exposure-response data were generally lacking, and potential confounding from other occupational exposures and behavioural factors was typically not controlled."

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 kidney 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 (1986b) study and "a tendency towards induction of lymphoid tumors in mice," citing subchronic studies (IARC, 1982, 1987). NTP (2021c) did not discuss kidney tumors.

8.4.6 Conclusions

Overall, governmental and international agencies did not conclude there was evidence for an association between benzene exposure and kidney cancer (ATSDR, 2007a, 2015, 2017a; US EPA, 1998; IARC, 2018; IOM, 2003, 2015; NRC, 2009). While some agencies discussed a few limited and largely null epidemiology studies, none of the agencies addressed animal or mechanistic evidence.

8.5 Conclusions

Government and scientific agencies conclude that there is no evidence to support an association between benzene and kidney cancer in humans (ATSDR, 2007a, 2015, 2017a; US EPA, 1998; IARC, 2018; IOM, 2003, 2015; NRC, 2009). There is no evidence that benzene causes kidney cancer in animal models, and the epidemiology evidence does not support an association. Most epidemiology studies reported risk estimates around 1 and, while some statistically significant associations were reported in a few studies, they were based on indirect or non-specific exposure measurements with no clear or compelling evidence that supports an exposure-response relationship. 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 support 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 the evidence does not support a causal association between benzene and kidney cancer.

9 Vinyl Chloride and Kidney Cancer

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

9.1 Epidemiology

9.1.1 Overview

I identified eight cohort studies that evaluated vinyl chloride exposure and kidney cancer; I did not identify any case-control studies. All these studies were conducted in the US and, collectively, they evaluated four unique populations. I review here all studies in populations at Camp Lejeune where vinyl chloride exposures were specified, even if overlapping, for completeness. I provide an overview, including a brief discussion of study characteristics and quality, below, and this is reviewed in more detail in Attachment C, Table C.1, and Attachment J, Table J.1. Study results are discussed briefly in Section 9.1.2 and reviewed in more detail in Attachment J, Table J.2. Epidemiology evidence is integrated with experimental evidence in Section 9.3.

9.1.1.1 Study Population

Vinyl chloride exposure and kidney cancer risk was evaluated in three studies of populations living or working at Camp Lejeune (Bove *et al*., 2014a,b; ATSDR, 2018b), one study of vinyl chloride or PVC resin manufacturing workers (Mundt *et al*., 2017), one study of workers at a chemical manufacturing plant (Carreón *et al*., 2014), and one study of employees of the Union Carbide Corporation's Chemicals and Plastics business group (Teta *et al*., 1990). Exposed and unexposed participants were selected from the same source population in all studies. Bove *et al*. (2014a,b) did not report whether any participants were excluded from their analyses and ATSDR (2018b) reported low participation rates. ATSDR (2018b) actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known, which increased the potential for selection bias. As discussed in Section 5, ATSDR (2018b) noted that in its Camp Lejeune study, selection bias could have biased results away from the null. Three of the studies reported <25% loss to follow-up (Carreón *et al*., 2014; Teta *et al*., 1990; Mundt *et al*., 2017).

9.1.1.2 Exposure Assessment

I assume that most participants in the Mundt *et al*. (2017), Carreón *et al*. (2014), and Teta *et al*. (1990) studies were exposed to vinyl chloride *via* inhalation or dermally, while exposures in the Camp Lejeune studies could have been *via* ingestion, inhalation, or dermal absorption.

The most critical limitation in all of the studies was the manner by which exposures were estimated. Three of the studies (Carreón *et al*., 2014; Teta *et al*., 1990; Mundt *et al*., 2017) assigned exposure based on whether someone was employed at a PVC factory for at least 1 year. Bove *et al*. (2014a,b) and ATSDR (2018b) 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). These were the only studies that considered the time-varying nature of the exposure. All three studies lacked 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*. (2014a,b) and ATSDR (2018b), which limits the interpretation of the reported chemical-specific results.

9.1.1.3 Outcome Assessment

Most data on kidney cancer outcomes were obtained or confirmed using reliable and complete methods based on identification from or confirmation in medical records, registries, or government databases (*e.g*., national death index). One study may have had incomplete ascertainment of cases, as it relied on self-report without another source of identification, such as a registry, to identify cases who did not self-report or who had died (ATSDR, 2018b).

One study examined kidney cancer incidence (ATSDR, 2018b), and the remaining five examined kidney cancer mortality. Because kidney cancer is not always fatal, analyses evaluating incidence are more informative than those evaluating mortality. All of the studies had sufficient follow-up time for cancer to develop (range: 9-72 years).

For all but one study (ATSDR, 2018b), data on kidney cancer outcomes were obtained or confirmed using reliable methods based on identification from or confirmation in medical records, registries, or government databases (*e.g*., national death index), resulting in complete or near complete ascertainment of cases. ATSDR (2018b) 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.

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 of the 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 obesity, hypertension, genetic factors, family history of kidney cancer, or diabetes. This is likely a reflection of the fact that many of these studies relied on registry or historical record data that did not capture information on these key variables. Only Bove *et al*. (2014b) collected and analyzed time-varying data (occupation, blue *vs.* white collar, as a proxy for other potential chemical exposures). Reporting on the degree or potential impact of missing covariate data varied.

None of the studies directly controlled for smoking. Bove *et al*. (2014a,b) attempted to consider the potential bias due to smoking through various means of examining the risk of cancers that are associated with smoking but not with solvents. There is no evidence that the lack of associations seen in those analyses or the adjustments of risk estimates for observed associations adequately addressed confounding by smoking.

Reporting on the degree or potential impact of missing covariate data varied. Also, 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 of the studies had documented exposures prior to the onset of disease. Bove *et al*. (2014a,b) appropriately incorporated 10-year lags into some of their analyses. ATSDR (2018b) and the other three studies did not consider disease latency in their analyses (Carreón *et al*., 2014; Teta *et al*., 1990; Mundt *et al*., 2017). The possible inclusion of cases in analyses that could have occurred within 4 years of participants' first exposures undermined their ability to properly assess an exposure-outcome relationship.

9.1.2 Study Results

The cohort studies reported risk estimates ranging from 0.39-1.84 for the relationship between vinyl chloride exposure and kidney cancer. The only exception is Bove *et al*. (2014b), which reported a risk estimate of infinity when comparing Camp Lejeune civilian employees with ≥ median maximum cumulative vinyl chloride exposure to those with < median maximum exposures because all kidney cancer deaths in civilian employees occurred in the higher exposure group.

The only statistically significant risk estimate was reported in ATSDR (2018b), in a comparison of Camp Lejeune Marines and Navy personnel with medium cumulative exposure to those with low cumulative exposure (OR = 1.45, 95% CI: 1.05-2.00). However, the risk estimate comparing those with high cumulative exposure to those with low cumulative exposure was not significant (OR = 1.55, 95% CI: 0.95-2.54) (ATSDR, 2018b). The exposure metric in these analyses was not specific to vinyl chloride because TCE, benzene, vinyl chloride, and TVOCs were correlated (gamma coefficient >0.99) so analyses were only conducted for TCE (ATSDR, 2018b). Bove *et al*. (2014a) did not report an association between vinyl chloride exposure and kidney cancer for Marines and Navy personnel at Camp Lejeune with high cumulative exposure compared to those with low cumulative exposure (HR = 1.51, 95% CI: 0.61-3.74) or when comparing Marines and Navy personnel at Camp Lejeune with medium/high cumulative to Marines and Navy personnel at Camp Pendleton (HR: 1.55, 95% CI: 0.94-2.57).

There was no association between working in vinyl chloride or PVC resin manufacturing (SMR = 1.16, 95% CI: 0.87-1.53) (Mundt *et al*., 2017), or working in a PVC, vinyl department, at a rubber and plastic chemical manufacturing plant (SMR = 0.64, 95% CI: 0.08-2.33) (Carreón *et al*., 2014) and kidney cancer risk. Teta *et al*. (1990) reported no association in hourly male employees in a Chemicals and Plastics business group (SMR = 1.74, 95% CI: 0.75-3.43).

One study discussed by Plaintiffs' experts evaluated vinyl chloride exposure and kidney cancer risk and was published before the start date of my literature search (Attachment A) but was not included in the agency reports I reviewed. Hu *et al*. (2002) evaluated incident kidney cancer cases diagnoses between 1994 and 1997 in Canada. They evaluated exposure to vinyl chloride using questionnaires on job history. They reported an increased risk of kidney cancer in men with any exposure to vinyl chloride (OR = 2.0, 95% CI: 1.2-3.3). They also reported an increased risk of kidney cancer associated with vinyl chloride exposures for at least 20 years (OR = 4.5, 95% CI: 1.9-10.6) but not for shorter durations. Like most of the epidemiology studies I reviewed, this study had major methodological limitations, including the potential for exposure misclassification and residual and uncontrolled confounding.

9.1.3 Conclusions

Vinyl chloride and kidney cancer associations were evaluated in six studies of four populations, three of which were at Camp Lejeune. Most analyses do not provide evidence of associations or exposure-response relationships. All of these studies had critical methodological limitations, including that only three assessed

vinyl chloride-specific concentrations in water, and these concentrations were not linked to individual water consumption data. All of the studies likely had residual and uncontrolled confounding. The high likelihood of exposure misclassification and confounding likely resulted in inaccurate or 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 kidney cancer.[13]

9.2 Toxicology

9.2.1 Animal Carcinogenicity Studies

I identified three oral, one intraperitoneal, and 17 chronic inhalation bioassays that stated they evaluated vinyl chloride exposure and the kidney. 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 bioassays in rats that stated they examined the kidney do not provide evidence that vinyl chloride is associated with kidney tumors. Feron *et al*. (1981) reported a single nephroblastoma among 80 male Wistar rats exposed to 14.1 ppm vinyl chloride and one nephroblastoma in a male control rat. No additional kidney tumors were reported in male or female 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 based on the point at which 75% of the control rats spontaneously died. Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) reported sporadic incidences of malignant kidney tumors, primarily nephroblastomas, in rats gavaged with doses up to 50 mg/kg-day, but these findings were not dose-related or due to treatment.

Among the 17 chronic inhalation bioassays in rats and mice, Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) reported sporadic incidences of benign (primarily kidney adenomas) and malignant (primarily nephroblastomas) kidney tumors in male and female Sprague-Dawley rats treated with 50-1,000 ppm vinyl chloride for 52 weeks. Benign and malignant kidney tumors were also reported in male and female Wistar rats treated with up to 10,000 ppm vinyl chloride for 52 weeks, but they were not treatment-related, as there was no dose-response. Kidney tumors were not reported in 15 other inhalation bioassays described in these papers, 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 but did not report any kidney tumor data for Sprague-Dawley rats of either sex.

9.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which vinyl chloride could cause kidney 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, 2024b; US EPA, 2000a; IARC, 2012b).

[13] The results from the study I identified from Plaintiffs' expert reports that was not included in the agency reports I reviewed (Section 9.1.2.) is consistent with my conclusions regarding vinyl chloride exposure and kidney cancer risk.

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 kidney 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 kidney, is unlikely to occur (US EPA, 2000a). Overall, there is no consistent or compelling evidence to support a biologically plausible mechanism by which vinyl chloride could cause kidney cancer.

9.3 Evidence Integration

A small number of epidemiology and toxicity studies have evaluated vinyl chloride exposure and kidney cancer (see Section 9.1 and 9.2). All of the epidemiology studies had higher-quality study designs (*i.e.*, cohort) and outcome assessments. The consideration of temporality, latency period, and control for potential confounders varied across studies, and none sufficiently controlled for all important potential confounders. 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 exposure and kidney cancer.

Table 9.1 Bradford Hill Assessment of Vinyl Chloride and Kidney Cancer

Aspect	Analysis
Strength of Association	The epidemiology evidence does not support a strong association between vinyl chloride exposure and kidney cancer.
Consistency	Risk estimates for vinyl chloride and kidney cancer were not consistently elevated.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between vinyl chloride and kidney cancer.
Temporality	Temporality was adequately addressed in some epidemiology studies, but only half appropriately considered a latency period.
Dose-Response	No epidemiology study reported a dose-response relationship between vinyl chloride exposure and kidney cancer.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which vinyl chloride could cause kidney cancer.
Coherence	Collectively, the evidence does not support a causal association between vinyl chloride exposure and kidney cancer. The majority of associations between vinyl chloride and kidney cancer in epidemiology studies were statistically null and both below and above 1, there were no consistent dose-response trends reported, and each study had several methodological limitations that impacted the interpretation of its results. There is no evidence for a plausible MoA for kidney cancer, and vinyl chloride did not cause kidney 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 kidney 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 (2017) 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 international agencies did not discuss kidney cancer in their reviews of vinyl chloride (ATSDR, 2024b, 2016, 2006; IARC, 2012b; NRC, 2009; IOM, 2003, 2015), except for US EPA (2000a), which stated, "No evidence for induction of kidney tumors in humans by VC has been reported." All of 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 stated 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 kidney cancer, nor did it discuss any epidemiology studies or animal bioassays that reported an increase in kidney tumors. In the subsequent "Addendum to the Toxicological Profile for Vinyl Chloride," ATSDR (2016) did not make additional conclusions regarding cancer.

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) did not discuss or draw any conclusions regarding vinyl chloride and kidney cancer.

In its most recent Toxicological Profile, ATSDR (2024b) maintained the conclusions of its 2006 evaluation, 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 (2024b) 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 (2024b) did not make a determination regarding kidney cancer, nor did it discuss any epidemiology studies or animal bioassays reporting an increase in kidney tumors. 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 kidney cancer.

9.4.2 NASEM

In its 2003 review, an IOM committee did not discuss animal or mechanistic data regarding kidney cancer. IOM (2003) concluded "there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to solvents under review, other than tetrachloroethylene and dry-cleaning solvents, and kidney cancer." NRC (2009) did not discuss any epidemiology, animal, or mechanistic studies regarding vinyl chloride and kidney cancer. IOM (2015) did not include any discussion of kidney 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 upon sufficient evidence for liver carcinogenicity in humans, consistent evidence of liver carcinogenicity in experimental animals, and supportive mechanistic evidence. US EPA (2000a) stated, "No evidence for induction of kidney tumors in humans by VC [vinyl chloride] has been reported." US EPA (2000a) did not discuss any animal or mechanistic evidence regarding vinyl chloride and kidney 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 kidney cancer.

In an updated evaluation, IARC (2012b) 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 (2012b) did not discuss any epidemiology, animal, or mechanistic evidence regarding kidney 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 DNA adducts. The etheno adducts can cause base pair substitutions, and to a lesser degree, frameshift mutations. NTP (2021d) stated that, "Inhalation exposure [to vinyl chloride] also caused… kidney tumors in rats." No additional epidemiology, animal, or mechanistic evidence was presented.

9.4.6 Conclusions

Government and international agencies did not discuss kidney cancer in their reviews of vinyl chloride (ATSDR, 2024b, 2016, 2006; IARC, 2012b; NRC, 2009; IOM, 2003, 2015), except for US EPA (2000a), which stated, "No evidence for induction of kidney tumors in humans by VC has been reported."

9.5 Conclusions

US EPA (2000a) stated, "No evidence for induction of kidney tumors in humans by VC has been reported." Other government and international agencies did not discuss kidney cancer in their reviews of vinyl chloride (ATSDR, 2006, 2016, 2024b; IARC, 2012b; NRC, 2009; IOM, 2003, 2015). Vinyl chloride does not cause kidney cancer in animal models, and there is no known biologically plausible MoA by which vinyl chloride could cause kidney cancer. Epidemiology studies reported risk estimates that were both below and above 1 and almost none were statistically significant. In addition, epidemiology evidence comes from 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 support associations or a dose-response relationship, (2) animal studies do not provide evidence of causation in humans, and (3) there is no proposed MoA with sufficient scientific support, I conclude the evidence does not support a causal association between vinyl chloride and kidney cancer.

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

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

I did not identify any epidemiology studies that investigated *trans*-1,2-DCE exposure and the risk of kidney 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 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 carcinogenicity 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 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). 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 exposure and kidney 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, 2000c, 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 indication of whether combined effects 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).

Although there is evidence that TCE can cause kidney cancer at very high occupational exposure levels, scientific evidence does not demonstrate that PCE, benzene, vinyl chloride, or *trans*-1,2-DCE can cause kidney cancer (discussed in Sections 6-9). Each of these chemicals targets different cell types and operates 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 kidney cancer causation.

12 Conclusions

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

TCE caused slight increases in kidney tumors in male rats, but not female rats or mice or hamsters of either sex. There is some evidence for a mutagenic MoA *via* glutathione-conjugation metabolites for TCE-induced kidney tumors. However, these metabolites are formed by a minor metabolic pathway in humans relative to oxidative metabolism, and there is some uncertainty as to whether TCE metabolism in humans is sufficient to support this MoA for kidney cancer. Associations between TCE exposure and kidney cancer in epidemiology studies were mostly above 1 but less than 2. Study limitations, particularly with respect to exposure estimates, make the interpretation of study results difficult. However, based on the relative consistency of kidney cancer risks >1, and the statistically significant increased risk in Charbotel *et al*. (2006), which has the most robust exposure estimates, the epidemiology evidence supports associations between kidney cancer and very high occupational TCE exposures (*e.g.*, >335 ppm-yr in Charbotel, *et al.*, 2006). Overall, government and international agencies conclude that there is evidence to support an association between TCE and kidney cancer in humans, primarily based on studies where participants had high occupational exposures.

Epidemiology studies of PCE and kidney cancer reported a wide range of risk estimates that were mostly null. The studies reporting risk estimates of a high magnitude, including the few statistically significant results, were unstable (based on wide CIs). There was no compelling evidence to support a dose-response relationship, and each study had several methodological limitations that impacted the interpretation of their results (particularly a high likelihood of exposure misclassification and uncontrolled confounding). Regarding experimental evidence, no chronic animal study reported a statistically significant increase of kidney tumors associated with oral or inhalation PCE exposure. There is no MoA with sufficient scientific support. Government and international agencies conclude that the scientific evidence does not support a likely association between PCE and kidney cancer in humans.

There is no evidence that benzene causes kidney cancer in animal models, and epidemiology evidence does not support an association. Most epidemiology studies reported risk estimates around 1; a few statistically significantly associations were reported, but only in studies with indirect or non-specific exposure measurements. In addition, most of the epidemiology studies have critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. Government and international agencies conclude that there is no evidence to support an association between benzene and kidney cancer in humans.

Vinyl chloride does not cause kidney cancer in animal models, and there is no known biologically plausible MoA by which vinyl chloride could cause kidney cancer. Most epidemiology studies reported risk

estimates that were null and close to 1. Risk estimates were both below and above 1, and almost no statistically significant associations were reported within or across studies, and none were specific to vinyl chloride. In addition, epidemiology evidence comes from studies with critical methodological limitations, including a high likelihood of exposure misclassification and uncontrolled confounding. Most government and international agencies did not discuss kidney cancer in their reviews of vinyl chloride; US EPA (2000a) stated, "No evidence for induction of kidney tumors in humans by VC has been reported."

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

My opinion is that, as a whole, the currently available scientific evidence provides support for an association between high occupational TCE exposures (*i.e.*, >335 ppm-yr) and kidney cancer, but does not support a causal association between PCE, benzene, vinyl chloride, or *trans*-1,2-DCE exposure and kidney cancer. 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 kidney 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 Kidney Cancer

A.1.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated trichloroethylene (TCE) and kidney cancer for various purposes (US EPA, 2011, 2020a; 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 kidney cancer, the searches identified epidemiology studies published from January 1, 2016 to November 17, 2023, and animal carcinogenicity and mode-of-action studies published from January 1, 2016 to November16, 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 ("Kidney Neoplasms"[Mesh] OR "kidney cancer*"[tw] OR "kidney cancer"[Title/Abstract:~2] OR "Carcinoma, Renal Cell"[Mesh] OR "Renal Cell Carcinoma") AND ("Humans"[MeSH] OR human OR humans 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 "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 "Cohort Study"[tw] OR "Case-Control Study"[tw] OR "Retrospective Study"[tw] OR "Longitudinal Study"[tw] OR "Cross-Sectional Study"[tw] OR "epidemiology" [Subheading] OR resident*)NOT (mice OR mouse OR rat OR rats OR rodent)

A.1.2.2 Animal Carcinogenicity and Mode of Action

(("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]) AND ((("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 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.1.3 Scopus Search Terms

A.1.3.1 Epidemiology

(TITLE-ABS-KEY ("kidney cancer*" OR {kidney cancer} OR "Renal Cell Carcinoma" OR {Renal Cell Carcinoma}) 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 group 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*)) AND ((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce AND ot AND 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 NOT TITLE-ABS (mice OR mouse OR rat OR rats OR rodent OR rodents) AND (LIMIT-TO (LANGUAGE , "English"))

A.1.3.2 Animal Carcinogenicity and Mode of Action

(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")) AND (((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce AND ot AND 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 (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*)) PUBYEAR > 2015

A.2 Perchloroethylene and Kidney Cancer

A.2.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated perchloroethylene (PCE) and kidney cancer for various purposes (US EPA, 2012, 2020b; 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 kidney cancer, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016 to 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

(("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]) AND ((("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[ti] OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene") OR 127-18-4[EC/RN Number]) OR (Ankilostin OR "Antisal 1"[tiab:~0] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "ENT 1860"[tiab:~0] 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 (("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.2.2.2 Animal Carcinogenicity and Mode of Action

(("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]) AND ((("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[ti] OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene") OR 127-18-4[EC/RN Number]) OR (Ankilostin OR "Antisal 1"[tiab:~0] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "ENT 1860"[tiab:~0] 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 ((((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.2.3 Scopus Search Terms

A.2.3.1 Epidemiology

(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")) AND (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 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.2.3.2 Animal Carcinogenicity and Mode of Action

(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")) AND (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 (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.3 Benzene and Kidney Cancer

A.3.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated benzene and kidney 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 kidney cancer, the searches identified all epidemiology, animal carcinogenicity, and mode-of-action studies published through November 17, 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

(("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]) 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

(("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]) 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 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.3.3 Scopus Search Terms

A.3.3.1 Epidemiology

(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")) AND (KEY (benzene) OR TITLE (benzene) OR CASREGNUMBER (71-43-2)) 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.3.3.2 Animal Carcinogenicity and Mode of Action

(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")) 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 Kidney Cancer

A.4.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated vinyl chloride and kidney cancer for various purposes (US EPA, 2000a,b; ATSDR, 2006, 2016, 2017a; IARC, 2012b). I then conducted literature searches using PubMed and Scopus. For vinyl chloride and kidney cancer, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published through November 17, 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

("Kidney Neoplasms"[MeSH Terms] OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "carcinoma, renal cell"[MeSH Terms] OR "Renal Cell Carcinoma"[Title/Abstract:~3] OR "nephroma, mesoblastic"[MeSH Terms] OR "Wilms Tumor"[MeSH Terms]) 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 (("Humans"[MeSH Terms] OR ("human s" OR "Humans"[MeSH Terms] OR "Humans" OR "human") OR ("human s" OR "Humans"[MeSH Terms] OR "Humans" OR "human") OR ("men"[MeSH Terms] OR "men") OR ("womans" OR "women"[MeSH Terms] OR "women" OR "woman" OR "women s" OR "womens") OR ("femal" OR "female"[MeSH Terms] OR "female" OR "females" OR "female s" OR "femals") OR ("male"[MeSH Terms] OR "male") OR "adult*" OR ("aged"[MeSH Terms] OR "aged" OR "elderly" OR "elderlies" OR "elderly s" OR "elderlys") OR ("populate" OR "populated" OR "populates" OR "populating" OR "population"[MeSH Terms] OR "population" OR "population groups"[MeSH Terms] OR ("population" AND "groups") OR "population groups" OR "populations" OR "population s" OR "populational" OR "populous") OR "epidemiolog*" OR "occupation*" OR "worker*" OR ("cohort" OR "cohort s" OR "cohorte" OR "cohorts") OR "Cohort Studies"[MeSH Terms] OR "Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms] OR "Case Reports"[Publication Type] OR "Retrospective Studies"[MeSH Terms] OR "Longitudinal Studies"[MeSH Terms] OR "Observational Study"[Publication Type] OR "Cross-Sectional Studies"[MeSH Terms] OR "Epidemiologic Studies"[MeSH Terms] OR "epidemiology"[MeSH Subheading]) NOT ("mice"[MeSH Terms] OR "mice" OR ("mice"[MeSH Terms] OR "mice" OR "mouse" OR "mouse s" OR "mouses") OR ("rats"[MeSH Terms] OR "rats" OR "rat") OR ("rats"[MeSH Terms] OR "rats") OR ("rodent s" OR "rodentia"[MeSH Terms] OR "rodentia" OR "rodent" OR "rodents"))))

A.4.2.2 Animal Carcinogenicity and Mode of Action

("Kidney Neoplasms"[MeSH Terms] OR "kidney cancer"[All Fields] OR "renal cancer"[All Fields] OR "kidney neoplasm"[All Fields] OR "renal neoplasms"[All Fields] OR "kidney tumor"[All Fields] OR "renal tumor"[All Fields] OR "carcinoma, renal cell"[MeSH Terms] OR "Renal Cell Carcinoma"[Title/Abstract:~3] OR "nephroma, mesoblastic"[MeSH Terms] OR "Wilms Tumor"[MeSH Terms]) AND (("vinyl chloride"[MeSH Terms] OR "vinyl chloride"[All Fields] OR ("chloroethenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethene"[All Fields]) OR ("chloroethylenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethylene"[All Fields]) OR "1-chloroethylene"[Title/Abstract:~0] OR (("ethylen"[All Fields] OR "ethylene"[Supplementary Concept] OR "ethylene"[All Fields] OR "ethylenes"[MeSH Terms] OR "ethylenes"[All Fields] OR "ethylene s"[All Fields] OR "ethylenic"[All Fields]) AND ("monochloride"[All Fields] OR "monochlorides"[All Fields])) OR ("monovinyl"[All Fields] AND ("chlorid"[All Fields] OR "chlorides"[MeSH Terms] OR "chlorides"[All Fields] OR "chloride"[All Fields])) OR "monochloroethene"[All Fields] OR "monochloroethylene"[All Fields] OR "Trovidur"[All Fields] OR "75-01-4"[EC/RN Number]) AND ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields] OR "toxicolog*"[All Fields] OR ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields]) OR ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields]) OR "carcinogen*"[All Fields] OR ("carcinogenesis"[MeSH Terms] OR "carcinogenesis"[All Fields] OR "carcinogeneses"[All Fields]) OR "cardiotox*"[All Fields] OR ("Pharmacokinetics"[MeSH Terms] OR "Pharmacokinetics"[All Fields] OR "toxicokinetic"[All Fields] OR "Pharmacokinetics"[MeSH Subheading] OR "Toxicokinetics"[All Fields] OR "Toxicokinetics"[MeSH Terms]) OR ("carcinogen s"[All Fields] OR "carcinogenes"[All Fields] OR "carcinogenic"[All Fields] OR "carcinogenically"[All Fields] OR "carcinogenicities"[All Fields] OR "carcinogenicity"[All Fields] OR "carcinogenity"[All Fields] OR "carcinogenous"[All Fields] OR "carcinogens"[Pharmacological Action] OR "carcinogens"[MeSH Terms] OR "carcinogens"[All Fields] OR "carcinogen"[All Fields]) OR ("embryolethal"[All Fields] OR "embryolethality"[All Fields]) OR "embryotox*"[All Fields] OR ("teratogenesis"[MeSH Terms] OR "teratogenesis"[All Fields] OR "teratogenicity"[All Fields] OR "teratogenic"[All Fields] OR "teratogenically"[All Fields] OR "teratogenity"[All Fields] OR "teratogenous"[All Fields] OR "Teratogens"[Pharmacological Action] OR "Teratogens"[MeSH Terms] OR "Teratogens"[All Fields] OR "teratogen"[All Fields]) OR "terato*"[All Fields] OR ("Mutagenesis"[MeSH Terms] OR "Mutagenesis"[All Fields] OR "mutageneses"[All Fields]) OR "Gene mutation"[All Fields] OR "Chromosome aberration"[All Fields] OR ("aneuploidy"[MeSH Terms] OR "aneuploidy"[All Fields] OR "aneuploidies"[All Fields]) OR ("polyploidy"[MeSH Terms] OR "polyploidy"[All Fields] OR "polyploidies"[All Fields]) OR "neurotox*"[All Fields] OR "nephrotox*"[All Fields] OR "immunotox*"[All Fields] OR "hepatotox*"[All Fields] OR "epigenetic*"[All Fields] OR "genotox*"[All Fields] OR "cytotox*"[All Fields] OR "Lethal dose"[All Fields] OR "PBPK"[All Fields] OR ("pharmacokinetic"[All Fields] OR "pharmacokinetical"[All Fields] OR "pharmacokinetically"[All Fields] OR "Pharmacokinetics"[MeSH Subheading] OR "Pharmacokinetics"[All Fields] OR "Pharmacokinetics"[MeSH Terms]) OR "dose response"[All Fields] OR "reference dose"[All Fields] OR "poison*"[All Fields] OR ("poisoned"[All Fields] OR "poisoning"[MeSH Terms] OR "poisoning"[All

Fields] OR "poisonings"[All Fields] OR "poisoning"[MeSH Subheading] OR "poisonous"[All Fields] OR "Poisons"[Pharmacological Action] OR "Poisons"[MeSH Terms] OR "Poisons"[All Fields] OR "poison"[All Fields]) OR "mutagen*"[All Fields] 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"[All Fields] AND "level"[All Fields]) OR "No-Observed-Adverse-Effect Level"[All Fields] OR "noael"[All Fields] OR "noaels"[All Fields]) 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*"[All Fields] OR ("teratogenesis"[MeSH Terms] OR "teratogenesis"[All Fields]) 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*"[All Fields] OR "mechanism*"[All Fields] OR "mode of action"[All Fields])))

A.4.3 Scopus Search Terms

A.4.3.1 Epidemiology

(TITLE-ABS ("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")) AND (TITLE-ABS ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR monochloroethylene OR trovidur)) AND (TITLE-ABS (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*)) AND (LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "MEDI"))

A.4.3.2 Animal Carcinogenicity and Mode of Action

(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")) 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 Kidney Cancer

A.5.1 Publication Date Range

I conducted literature searches using PubMed and Scopus for epidemiology and toxicity 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

List of Tables

Table B.1	Camp Lejeune Cohort Study Characteristics
Table B.2	Employment/Assignment at Camp Lejeune and Kidney Cancer Risk
Table B.3	TCE Exposure at Camp Lejeune and Kidney Cancer Risk
Table B.4	PCE Exposure at Camp Lejeune and Kidney Cancer Risk
Table B.5	Benzene Exposure at Camp Lejeune and Kidney Cancer Risk
Table B.6	Vinyl Chloride Exposure at Camp Lejeune and Kidney Cancer Risk

Table B.1 Camp Lejeune Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Bove *et al.* (2014a)	US	Marines & Navy personnel at CL and CP	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	Kidney	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[a] CP: 34-60[a]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Kidney	SSA and NDI	1979-2008
ATSDR (2018b)[b]	US	Marines & Navy personnel and civilian employees at CL and CP	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	Kidney	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Bove *et al.* (2024a)	US	Marines & Navy personnel and civilian employees at CL and CP	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: 232,026 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	Kidney; kidney & renal pelvis	SSA Data for Epidemiological Researchers and NDI	1979-2018
Bove *et al.* (2024b)	US	Marines & Navy personnel and civilian employees at CL and CP	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	Kidney & renal pelvis; renal cell & clear cell carcinoma; renal cell carcinoma, NOS; clear cell only; papillary	SSA Data for Epidemiological Researchers, NDI, and cancer registries (state, territory, DOD, and VA)	1996-2017

Notes (continued on next page):

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; NOS = Not Otherwise Specified; SSA = Social Security Administration; US = United States; VA = Veterans Affairs; Yrs = Years.
$\bar{x}$ = Mean.
(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, 2018b).
(c) Median age at survey or death (ATSDR, 2018b).
(d) Bove *et al*. (2024a) 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 Kidney Cancer Risk

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
Bove *et al.* (2014a)	US general population	Mort	SMR	**CL Marines & Navy Personnel**					Age, sex, race, and calendar period
				All	42	36.08	1.16 (0.84-1.57)	–	
	CP Marines & Navy personnel		HR	All (10-yr lag)	42	–	1.35 (0.84-2.16)		Age, sex, race, rank, and education
Bove *et al.* (2014b)	US general population	Mort	SMR	**CL Civilian Employees**					Age, sex, race, and calendar period
				All	7	5.40	1.30 (0.52-2.67)	–	
	CP civilian employees		HR	All (10-yr lag)	7	–	1.92 (0.58-6.34)		Age, sex, race, blue- or white-collar occupation, and education
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age
				All	192	–	1.31 (0.86-1.99)	–	
	CP civilian employees			**CL Civilian Employees**					
				All	20	–	1.52 (0.69-3.35)	–	
Bove *et al.* (2024a)[b,c]	US general population	Mort	SMR	**CL Marines & Navy Personnel**					Age, sex, race, and calendar period
				Began active duty between 1975-1985	139	–	1.11 (0.93-1.31)	–	
				All	279		1.13 (1.00-1.27)		
	CP Marines & Navy personnel		RR	Began active duty between 1975-1985	139		1.21 (0.95-1.54)		Age, sex, and race
				All	279		**1.22 (1.03-1.45)**		
			HR	Began active duty between 1975-1985	139		1.21 (0.95-1.54)		Age, sex, race, rank, and education level
				All	279		**1.21 (1.02-1.43)**		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	1.33 (0.95-1.86)	–	
				Medium (>2-7)			1.23 (0.88-1.72)		
				High (>7)			1.04 (0.73-1.49)		
	US general population		SMR	**CL Civilian Workers**					Age, sex, race, and calendar period
	CP civilian workers			All	24	–	1.16 (0.74-1.73)	–	
			RR		24		1.49 (0.76-2.92)		Age, sex, and race
			HR		24		1.44 (0.73-2.84)		Age, sex, race, blue collar work, and education level
				Duration of assignment (quarter yrs)					
				Low (1-5)	–	–	1.36 (0.48-3.82)	–	

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
				Medium (6-22)			1.36 (0.54-3.41)		
				High (23-53)			1.68 (0.75-3.76)[d]		
Bove *et al.* (2024b)[b]	CP Marines & Navy personnel	Inc	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education level
				Personnel who began active duty between 1975-1985, by type of kidney & renal pelvis cancer					
				Kidney & renal pelvis	710	–	1.06 (0.95-1.18)	–	
				Renal cell & clear cell carcinoma	524		1.03 (0.91-1.16)		
				RCC, NOS	250		1.12 (0.94-1.34)		
				Clear cell only	277		0.97 (0.82-1.14)		
				Papillary	92		1.18 (0.86-1.60)		
				All personnel, by type of kidney & renal pelvis cancer					
				Kidney & renal pelvis	1,211	–	1.04 (0.96-1.12)	–	
				Renal cell & clear cell carcinoma	879		1.00 (0.91-1.09)		
				RCC, NOS	448		1.09 (0.96-1.25)		
				Clear cell only	437		0.92 (0.81-1.04)		
				Papillary	162		1.11 (0.89-1.40)		
				Personnel who began active duty between 1975-1985, by type of kidney & renal pelvis cancer and duration of assignment (quarter yrs)					
				Kidney & renal pelvis					
				Low (1-6)	431	–	1.12 (0.99-1.27)	–	
				Medium (7-10)	152		1.01 (0.84-1.20)		
				High (>10)	127		0.94 (0.77-1.16)		
				RCC & clear cell					
				Low (1-6)	317	–	1.07 (0.93-1.23)	–	
				Medium (7-10)	109		0.97 (0.78-1.19)		
				High (>10)	98		1.00 (0.79-1.26)		
				RCC-NOS					
				Low (1-6)	147	–	1.12 (0.91-1.38)	–	
				Medium (7-10)	57		1.16 (0.86-1.55)		
				High (>10)	46		1.03 (0.73-1.46)		
				Clear cell only					
				Low (1-6)	171	–	1.03 (0.85-1.24)	–	
				Medium (7-10)	53		0.83 (0.62-1.11)		

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
				High (>10)	53		0.97 (0.71-1.34)		
				Papillary					
				Low (1-6)	55	–	1.28 (0.90-1.83)	–	
				Medium (7-10)	21		1.13 (0.69-1.85)		
				High (>10)	16		0.84 (0.47-1.52)		
	CP civilian workers			**CL Civilian Workers**					Age, sex, race, blue collar work, and education level
				Type of kidney & renal pelvis cancer					
				Kidney & renal pelvis	58	–	1.12 (0.76-1.67)	–	
				Renal cell & clear cell carcinoma	43		1.05 (0.67-1.66)		
				RCC, NOS	28		1.18 (0.65-2.13)		
				Clear cell only	15		0.89 (0.44-1.82)		
				Papillary	3		0.96 (0.18-5.27)		
				Type of kidney & renal pelvis cancer and duration of employment (quarter yrs)					
				Kidney & renal pelvis					
				Low/medium (1-21)	30	–	0.91 (0.56-1.48)	–	
				High (>21)	28		1.70 (0.93-3.13)		
				RCC & clear cell					
				Low/medium (1-21)	21	–	0.88 (0.49-1.56)	–	
				High (>21)	22		1.36 (0.69-2.69)		
				RCC-NOS					
				Low/medium (1-21)	14	–	1.03 (0.49-2.15)	–	
				High (>21)	14		1.48 (0.61-3.64)		
				Clear cell only					
				Low/medium (1-21)	7	–	0.67 (0.26-1.72)	–	
				High (>21)	8		1.24 (0.44-3.52)		
				Papillary					
				Low/medium (1-21)	1	–	0.51 (0.05-4.97)	–	
				High (>21)	2		1.41 (0.24-8.46)		

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; NOS = Not Otherwise Specified; OR = Odds Ratio; RCC = Renal 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,b) also ran quantitative bias analyses of exposure misclassification and unmeasured confounding from smoking; however, they found that the impacts would likely be minor and may cancel each other out.
(c) Bove *et al*. (2024a) also ran analyses based on contributing causes, which I do not report here.
(d) Bove *et al*. (2024a) reported a "monotonic trend was observed for kidney cancer, with low duration HR of 1.36 (95% CI: 0.48, 3.82) and high duration of 1.68 (95% CI: 0.75, 3.76)." This trend was not evaluated for statistical significance.

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

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Bove *et al.* (2014a)	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)[a]	23	–	0.95 (0.48-1.86)	–	
				Medium/high (>3,100-8,585)[a]	19		1.50 (0.91-2.49)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-3,100)	11		1.54 (0.65-3.61)		
				Medium (>3,100-7,700)	8		1.21 (0.47-11.46)		
				High (>7,700-39,745)	11		1.52 (0.64-3.61)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**Maximum Cumulative Exposure Level with 10-Yr Lag[b]**					Age, sex, race, blue- or white-collar occupation, and education
				≥Median	7	0	∞	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**Cumulative Exposure Level (µg/L-mos)[c]**					Age and sex
				CL Marines & Navy personnel[d]					
				Low (<110)	82	–	0.90 (0.56-1.45)	–	
				Medium (110-<11,030)	86		1.33 (0.84-2.13)		
				High (≥11,030)	24		1.42 (0.78-2.58)		
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)[e]			Medium (110-<11,030)	86		**1.45 (1.05-2.00)**		
				High (≥11,030)	24		1.55 (0.95-2.54)		
	CP civilian employees			*CL civilian employees[f]*					Age
				Low (<10,868)	3	–	0.34 (0.09-1.25)	–	
				Medium (10,868-<50,563)	8		1.80 (0.68-4.76)		
				High (≥50,563)	9		**13.92 (5.09-38.10)**		
	CL civilian employees with low exposure (<10,868 µg/L-mos)[e]			Medium (10,868-<50,563)	8		**5.34 (1.38-20.6)**		
				High (≥50,563)	9		41.54 (0.30-76.10)		

Notes (continued on next page):

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.
Bolded values indicate statistical significance.
(a) Exposure groups are unclear in Bove *et al*. (2014a). 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*. (2014a,b) evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.
(c) 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, 2018b).
(d) 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).
(e) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.
(f) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table B.4 PCE Exposure at Camp Lejeune and Kidney 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.* (2014a)	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)[a]	20	–	0.91 (0.46-1.78)	–	
				Medium/high (>155-8,585)[a]	22		1.55 (0.94-2.57)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-155)	8		1.40 (0.54-3.58)		
				Medium (>155-380)	11		1.82 (0.75-4.42)		
				High (>380-8,585)	11		1.59 (0.66-3.86)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**Cumulative Exposure Level (µg/L-mos) with 10-Yr Lag[b]**					Age, sex, race, blue- or white-collar occupation, and education
				≥Median	7	0	∞	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**Cumulative Exposure Level (µg/L-mos)[c]**					Age and sex
				CL Marines & Navy personnel					
				Low (0-<36)	80	–	0.88 (0.55-1.41)	–	
				Medium (36-<711)	80		1.28 (0.79-2.05)		
				High (≥711)	32		1.79 (1.02-3.12)		
	CL Marines & Navy personnel with low exposure (>0-<36 µg/L-mos)[d]			Medium (36-<711)	80		**1.43 (1.02-2.00)**		
				High (≥711)	32		**2.01 (1.29-3.13)**		
	CP civilian employees			*CL civilian employees[e]*					Age
				Low (<457)	3	–	0.34 (0.09-1.25)	–	
				Medium (457-<2,118)	8		1.80 (0.68-4.76)		
				High (≥2,118)	9		**13.92 (5.09-38.10)**		
	CL civilian employees with low exposure (<457 µg/L-mos)[d]			Medium (457-<2,118)	8		**5.34 (1.38-20.6)**		
				High (≥2,118)	9		41.54 (0.30-76.10)		

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; TCE = Trichloroethylene; 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*. (2014a). 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*. (2014a,b) evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant.

(c) ATSDR (2018b) 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) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

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

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

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Covariates Controlled For
Bove *et al.* (2014a)	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)[a]	22	–	1.03 (0.54-1.94)	–	
				Medium/high (>45-601)[a]	20		1.48 (0.88-2.47)		
	CL Marines & Navy personnel with exposure <2 µg/L-mos[b]			Low (2-45)	8		1.31 (0.52-3.29)		
				Medium (>45-110)	10		1.38 (0.58-3.28)		
				High (>110-601)	10		1.36 (0.57-3.25)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**Cumulative Exposure Level (µg/L-mos) with 10-Yr Lag[b]**					Age, sex, race, blue- or white-collar occupation, and education
				≥Median	5	–	1.82 (0.34-9.78)	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel[c]**					Age and sex
				Cumulative exposure level[d]					
				Low	82	–	0.90 (0.56-1.45)	–	
				Medium	86		1.33 (0.84-2.13)		
				High	24		1.42 (0.78-2.58)		
	CL Marines & Navy personnel with low exposure[e]			Medium	86		**1.45 (1.05-2.00)**		
				High	24		1.55 (0.95-2.54)		

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.* (2014a). 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.* (2014a,b) evaluated continuous and log10 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, 2018b).
(d) ATSDR (2018b) 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, 2018b).
(e) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

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

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	*p*-trend	Variables Adjusted For
Bove *et al.* (2014a)	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)[a]	22	–	0.91 (0.46-1.78)	–	
				Medium/high (>205-2,800)[a]	20		1.55 (0.94-2.57)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-205)	10		1.66 (0.68-4.04)		
				Medium (>205-500)	10		1.61 (0.65-3.98)		
				High (>500-2,800)	10		1.51 (0.61-3.74)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**Maximum Cumulative Exposure Level with 10-Yr Lag[c]**					Age, sex, race, blue- or white-collar occupation, and education
				≥Median	7	0	∞	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel[c]**					Age and sex
				Cumulative exposure level[d]					
				Low	88	–	0.90 (0.56-1.45)	–	
				Medium	83		1.33 (0.84-2.13)		
				High	11		1.42 (0.78-2.58)		
	CL Marines & Navy personnel with low exposure[e]			Medium	83		**1.45 (1.05-2.00)**		
				High	11		1.55 (0.95-2.54)		

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.* (2014a). 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.* (2014a,b) evaluated continuous and log10 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, 2018b).
(d) ATSDR (2018b) 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, 2018b).
(e) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

Attachment C

Epidemiology Study Quality Assessment

List of Tables

Table C.1 Kidney Cancer Epidemiology Study Quality Assessment

Table C.1 Kidney Cancer Epidemiology Study Quality Assessment

Study	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		Strengths • Appropriate study and comparison groups • 2.3% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure estimate (*i.e.*, considered frequency, duration, and intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • Indirect chemical exposure measurement (*i.e.*, work location/type of work, and uniform task approach)	Strengths • Deaths identified using reliable sources (*i.e.*, company records, SSA, DMV, and death certificates) • 32 yrs of follow-up Weaknesses • Assessed mortality only • 2.2% of all deaths without death certificate (1.1% in continuously exposed group, 1.3% in intermittently exposed group, and 4.3% in unexposed group)	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • About 8% missing race data; assumed white	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10-19 and 20 years) Weaknesses • No major weaknesses
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 Weaknesses • Indirect chemical exposure measurement (*i.e.*, factory personnel records) • Qualitative exposure estimate (*i.e.*, ever employment at	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, California DMV, credit records, death certificates, California Death Tapes) • 25 yrs of follow-up Weaknesses	Strengths • Controlled for age, sex, and race Weaknesses • Did not control for or consider smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 4-year lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							manufacturing plant) • Did not assess time-varying nature of exposure	• Assessed mortality only	consumption, or other occupational exposures • Race was missing for unspecified number of subjects; assumed to be white	
Blair *et al.* (1989)	Coast Guard officers and personnel	T	P	B		Strengths • Appropriate study and comparison groups • 4% loss to follow-up Weaknesses • Unknown number of exclusions	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 • ≈8.5% 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • 8% missing race data; assumed white	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
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-	Strengths • No missing data Weaknesses • Indirect chemical exposure measurements (*i.e.*, business group) • Qualitative exposure estimate (*i.e.*,	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, NDI, company mortality register, benefit records, and death certificates) • 10 yrs of follow-up Weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension,	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						white employee mortality compared to white-only population) • Unknown number of exclusions	employment in group) • Did not assess time-varying nature of exposure	• Assessed mortality only •	genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	
Dagg *et al.* (1992)	Employees at oil refineries, US			B		<u>Strengths</u> • 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) <u>Weaknesses</u> • All women excluded (4.8% of total) due too few cases	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, California death index, and Equifax) • 37 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age, sex, and race/ethnicity • No missing data <u>Weaknesses</u> • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (*e.g.*, analyses based on 10-19, 20-29, and ≥30 yrs since hire) <u>Weaknesses</u> • No major weaknesses
Sinks *et al.* (1992)	Paperboard printing plant workers	T				<u>Strengths</u> • Appropriate study and comparison groups • 10% lost to follow-up • <2% excluded in SMR analyses and <16% excluded in SIR analyses	<u>Strengths</u> • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, employment at facility)	<u>Strengths</u> • All deaths and cases identified and validated using reliable sources (*i.e.*, SSA, mailing address with USPS, death certificates, company medical	<u>Strengths</u> • Controlled for: age, sex, and race <u>Weaknesses</u> • Did not control for or consider: smoking, obesity, hypertension, genetic factors,	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency in SIR or SMR analyses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						<u>Weaknesses</u> • No major weaknesses	• Qualitative exposure estimate (*i.e.*, any employment) • Did not assess time-varying nature of exposure	records, and local cancer registries) • Assessed disease incidence • 32 yrs of follow-up <u>Weaknesses</u> • Could not obtain death certificates for 17% of participants known to have died	family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • 85% missing race data; assumed white	
Rushton (1993)	Oil refinery and petroleum distribution workers, UK			B		<u>Strengths</u> • Appropriate study and comparison groups • 3.8% loss to follow-up <u>Weaknesses</u> • Unknown number of exclusions	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, National Health Service Central Register and death certificates) • 14 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age and sex • No missing data <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses based on 10+ yrs since first exposure) <u>Weaknesses</u> • No major weaknesses
Tsai *et al.* (1993)	Male refinery/ petrochemical workers, US			B		<u>Strengths</u> • Appropriate study and comparison groups • No loss to follow-up	<u>Strengths</u> • No missing data <u>Weaknesses</u> • Indirect benzene exposure	<u>Strengths</u> • Deaths identified or using reliable source (*i.e.*, company records, NDI, and SSA)	<u>Strengths</u> • Controlled for: age, sex, race/ethnicity <u>Weaknesses</u>	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u>

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						Weaknesses • No major weaknesses	measurement (*i.e.*, job history) • Qualitative exposure estimate (*i.e.*, ever/never employment) • Did not assess time-varying nature of exposure	• 17 yrs of follow-up Weaknesses • Assessed mortality only	• Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data unknown	• No consideration of latency
Wong *et al.* (1993)	Petroleum marketing/ distribution workers			B		Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up and number of exclusions	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, frequency and intensity) • Assessed time-varying nature of exposure • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment records, job titles, work history, and JEM)	Strengths • Cases identified using reliable sources (*i.e.*, SSA, DMF, NDI, company records, state vital statistics departments, and death certificates) • 43 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • 40% missing race data (assumed White)	Strengths • Exposure documented before outcome • Appropriate consideration of latency (analyses based on 5-9, 10-19, 20-29, and 30+ yrs since first exposure) Weaknesses • No major weaknesses
Axelson *et al.* (1994)	TCE-exposed workers	T				Strengths	Strengths • Direct chemical exposure	Strengths • Cases identified using reliable	Strengths • Controlled for: age and sex	Strengths

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• Appropriate study and comparison groups • <4% excluded Weaknesses • Unknown loss to follow-up	measurement (*i.e.*, U-TCA) used to form study population • No missing data Weaknesses • Qualitative exposure estimate (*i.e.*, ever exposure) • Did not assess time-varying nature of exposure	sources (*i.e.*, Swedish cause-of-death and cancer registries) • Assessed disease incidence • 30 yrs of follow-up Weaknesses • No major weaknesses	• No missing data Weaknesses • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• Exposure documented before outcome Weaknesses • No consideration of latency
Anttila *et al.* (1995)	FIOH workers	T	P			Strengths • Appropriate study and comparison groups • No loss to follow-up; 7% excluded (*i.e.*, inability to match samples to individual) Weaknesses • No major weaknesses	Strengths • Direct chemical exposure measurement (*i.e.*, U-TCA) used to form study population • 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (10- and 20-yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Henschler *et al.* (1995a)	Cardboard factory workers	T				Strengths • Appropriate study group and comparison groups • About 8% excluded (*i.e.*, refused to participate or not able to participate due to poor physical health) or lost to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect exposure measurement (*i.e.*, job location) • Qualitative exposure estimate (*i.e.*, ever exposure) • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using reliable sources (*i.e.*, medical, personnel, and pension records) and all renal cell tumors verified by histopathological examination • Assessed disease incidence • 36 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • All cases occurred 18+ yrs after first exposure 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.*, employment at the plant) • Qualitative exposure estimate (*i.e.*, ever employed 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/ethnicity • No missing data Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									occupational exposures	
Collingwood *et al.* (1996)	Workers at an oil refinery, US			B		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.*, 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: age, sex, and race • About 3.5% missing race data; classified as White Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses of 20-29 and 30+ yrs since first employment) Weaknesses • No major weaknesses
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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol	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

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									consumption, or other potential occupational exposures • Amount of missing data unknown	
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 • No major weaknesses	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 reliable sources (*i.e.*, cancer registries) • Assessed disease incidence • ≥5 years follow-up (Denmark: 18yrs; Finland: 16 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
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	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, NDI, and death certificates) • 44 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age and sex Weaknesses • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors,	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							measurement (*i.e.*, job classification and JEM) • Did not assess time-varying nature of exposure	• About 3% of deaths missing death certificates; unclear how this was handled in analysis	family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Considered race but data was "sparse" and was ultimately not used	
Pukkala (1998)	Employees of a Finnish oil and chemical enterprise			B		<u>Strengths</u> • Appropriate study and comparison groups • No loss to follow-up/exclusions <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect benzene exposure measurement (*i.e.*, work history and job categories) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, Finnish Cancer Registry) • Assessed disease incidence • 24 yrs of follow-up <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Controlled for: age and sex, • No missing data <u>Weaknesses</u> • Did not consider or control for: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure data collected prior to outcome • Appropriate consideration of latency (*i.e.*, analyses of 5-14 yrs since first employment) <u>Weaknesses</u> • No major weaknesses
Bulbulyan *et al.* (1999)	Female Russian printing plant employees			B		<u>Strengths</u> • 1.5% loss to follow-up (1.5%) and no exclusions <u>Weaknesses</u> • Inappropriate comparison group	<u>Strengths</u> • No missing data <u>Weaknesses</u> • Indirect benzene exposure measurement (*i.e.*,	<u>Strengths</u> • Deaths identified using a reliable source (*i.e.*, Moscow Vital Statistics Department) • 15 yrs follow-up	<u>Strengths</u> • Controlled for: age and sex • No missing data <u>Weaknesses</u> • Did not control for or consider:	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (benzene

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						(*i.e.*, Moscow reference rates were based on only a single year during follow-up, 1992) • Notable weakness in study population (*i.e.*, benzene use in bookbinding was discontinued in 1958, but results stratified by year of first employment are not provided)	personnel records and job type) • Qualitative exposure estimate (*i.e.*, job type) • Did not assess time-varying nature of exposure	Weaknesses • Assessed mortality only	race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Did not include relevant covariates in a time-varying manner	use discontinued 20 yrs prior) Weaknesses • No major weaknesses
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 • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect exposure measurement (*i.e.*, based on job histories) • 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (lag 0-30+ yrs) Weaknesses • No major weaknesses
Divine *et al.* (1999)	Employees at refineries, petrochemical			B		Strengths	Strengths • Semiquantitative exposure	Strengths • Deaths identified using reliable	Strengths	Strengths

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
	facilities and research laboratories, US					• Appropriate study and comparison groups • 2.5% loss to follow-up Weaknesses • Unknown number of exclusions	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	sources (*i.e.*, company records, NDI, SSA, HCFA, and death certificates) • 47 yrs of follow-up Weaknesses • Assessed mortality only	• Controlled for or considered: age, sex, and race • 1% missing data on sex or race, assumed to be male and/or White Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• Exposure documented before outcome • Appropriate consideration of latency (had to be employed ≥5 yrs) Weaknesses • No major weaknesses
Ritz (1999)	Uranium-processing workers	T				Strengths • Appropriate study and comparison groups • 8% excluded (*i.e.*, not matched in records) 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									occupational exposures	
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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Hansen *et al.* (2001)	TCE exposed workers	T				Strengths • Appropriate sample and comparison groups Weaknesses • Loss to follow-up unknown; unable to match individual for 36% and 48% of urine and air samples, respectively	Strengths • Direct chemical exposure measurement (*i.e.*, U-TCA and occupational air measurements) used to form study population • No missing data Weaknesses • Qualitative exposure estimate (*i.e.*, any 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential	Strengths • Appropriate consideration of latency (10- and 20-yr lags) Weaknesses • Exposure period overlaps period of follow-up; unclear how this was handled in analysis

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Did not assess time-varying nature of exposure		occupational exposures	
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.*, company records, PBI, SSA NDI/NDI Plus, and death certificates) • 38 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for or considered: age, sex, and race5% missing race (assumed White) Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	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
Wong *et al.* (2001b)	Employees at an oil refinery, US			B		Strengths • Appropriate study and comparison groups • 1.7% 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)	Strengths • Deaths identified using reliable sources (*i.e.*, company records, PBI, SSA, NDI/NDI Plus, and death certificates) • 51 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race5% missing race (assumed White) Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer,	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses considering 20-39 and 40+ yrs since first employment; 10-29 and 30+ yrs of employment)

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Did not assess time-varying nature of exposure		diabetes, alcohol consumption, or other potential occupational exposures	<u>Weaknesses</u> • No major weaknesses
Sorahan *et al.* (2002)	Refinery and petroleum distribution workers, UK			B		<u>Strengths</u> • Appropriate study and comparison groups <u>Weaknesses</u> • Unknown loss to follow-up	<u>Strengths</u> • No major strengths <u>Weaknesses</u> • Indirect chemical exposure measurement-based on job history • Qualitative exposure estimate (*i.e.*, employment as refinery or distribution worker) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, national registers and death certificates) • 48 years of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age and sex <u>Weaknesses</u> • 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 unknown	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency
Travier *et al.* (2002)	Dry-cleaning workers	T	P			<u>Strengths</u> • Appropriate study and comparison groups <u>Weaknesses</u> • Loss to follow-up and number of exclusions unknown	<u>Strengths</u> • No major strengths <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported employment and industrial codes from two decennial censuses)	<u>Strengths</u> • Cases and death identified from a reliable source (*i.e.*, CERIII) • Assessed disease incidence • 19 yrs of follow-up <u>Weaknesses</u> No major weaknesses	<u>Strengths</u> • Controlled for: age and sex • No missing data <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors,	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Qualitative exposure estimate (*i.e.*, job title) • Amount of missing data unknown • Did not assess time-varying nature of exposure		family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	
Chang *et al.* (2003)	Electronics factory workers	T	P			<u>Strengths</u> • Appropriate study and comparison groups • No loss to follow-up or exclusions <u>Weaknesses</u> • Relatively young subjects (mean age 39 yrs at end of follow-up)	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, ever employment at factory) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Deaths identified and validated using a reliable source (*i.e.*, National Mortality Database) • 13 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only •	<u>Strengths</u> • Controlled for: age and sex • No missing data <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (analyses by duration 5+ yrs) <u>Weaknesses</u> • No major weaknesses
Lewis *et al.* (2003)	Canadian refinery/ petrochemical workers			B		<u>Strengths</u> • Appropriate study and comparison groups • No loss to follow-up <u>Weaknesses</u> • Young study population at cohort inception	<u>Strengths</u> • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect benzene exposure	<u>Strengths</u> • Cases identified using a reliable source (*i.e.*, Canadian Cancer Data Base); deaths identified using a reliable source (*i.e.*, Canadian Mortality Data Base)	<u>Strengths</u> • Controlled for: age and sex <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, obesity, hypertension,	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (analyses by duration 5+ yrs) <u>Weaknesses</u>

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						(Male $\bar{x}$ = 29.1; Female $\bar{x}$ = 27.5)	measurement (*i.e.*, location, department, function, date, and expert review) • Did not assess time-varying nature of exposure	• Assessed disease incidence • 31 yrs of follow-up Weaknesses • No major weaknesses	genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• No major weaknesses
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 • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment and blue-collar status at companies) • 37% of workers for whom blue- or white-collar status unknown (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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Appropriate consideration of latency (20-yr lag) Weaknesses • Exposure period overlaps period of follow-up; unclear how this was handled in analysis
Tsai *et al.* (2003)	Male chemical/ refinery workers, US			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, and SSA) • 27 yrs of follow-up	Strengths • Controlled for: age, sex, race/ethnicity, obesity, and hypertension Weaknesses	Strengths • Exposure documented before outcome • Sufficient consideration of latency (*i.e.*,

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• No major weaknesses	Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Did not assess time-varying nature of exposure	Weaknesses • Assessed mortality only	• Did not control for or consider: smoking, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data unknown	conducted a sensitivity analysis for cancers with shorter latencies) Weaknesses • No major weaknesses
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 • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, company records and work histories) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, benefit records, NDI, SSA, and death certificates) • 28 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses considering only employees hired before 1950; 15-29 and 30+ yrs of employment) Weaknesses • No major weaknesses
Ji *et al.* (2005)	Swedish working population	T				Strengths • Appropriate study and comparison groups • No loss to follow-up or exclusions	Strengths • No missing data Weaknesses • Indirect chemical exposure	Strengths • Cases identified using a reliable source (*i.e.*, Swedish Cancer Registry)	Strengths • Controlled for: age and sex • No missing data Weaknesses	Strengths • Exposure documented before outcome Weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						<u>Weaknesses</u> • No major weaknesses	measurement (*i.e.*, self-reported occupation on decennial censuses) • Qualitative exposure estimate (*i.e.*, job title) • Did not assess time-varying nature of exposure	• Assessed disease incidence • 40 yrs of follow-up <u>Weaknesses</u> • No major weaknesses	• Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• No consideration of latency
Sorahan *et al.* (2005)	Benzene exposed workers			B		<u>Strengths</u> • Appropriate study and comparison group • 5.7% loss to follow-up <u>Weaknesses</u> • Unknown number of exclusions • Follow-up did not end with first cancer incidence	<u>Strengths</u> • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, personnel officer reports at firms or plants) • Qualitative exposure estimate (*i.e.*, ever exposure) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Cases and deaths identified and confirmed using reliable sources (*i.e.*, ONS and DHSS) • Assessed disease incidence • 31 and 35 yrs of follow-up for incidence and mortality, respectively <u>Weaknesses</u> • Diagnoses unconfirmed for 22 cases	<u>Strengths</u> • Controlled for: age and sex • No missing data <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency
Zhao *et al.* (2005)	Aerospace workers	T				<u>Strengths</u> • Appropriate study and comparison groups	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, state cancer registries,	<u>Strengths</u> • Controlled for: age, sex, and all other chemical exposures of interest (*i.e.*,	<u>Strengths</u> • Exposure documented before outcome

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• <1% excluded (*i.e.*, missing employment information) Weaknesses • No major weaknesses	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	company records, SSA, CA vital statistics, NDI records, and death certificates • Assessed disease incidence • 52 and 13 yrs of follow-up for mortality and incidence, respectively Weaknesses • Not all cancer cases were identified; only covered eight states outside of CA	PAHs, benzene, mineral oils, and hydrazine) • No missing data Weaknesses • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, or alcohol consumption • Did not include relevant covariates in a time-varying manner (*i.e.*, other chemical exposures)	• Appropriate consideration of latency (20-yr lag) Weaknesses • No major weaknesses
Sung *et al.* (2007)	Female electronics factory workers	T				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)	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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Did not assess time-varying nature of exposure		consumption, or other potential occupational exposures	
Boice *et al.* (2006)	Aerospace workers	T				Strengths • Appropriate study and comparison groups • <1% loss to follow-up; about 12% excluded (*i.e.*, employees engaged in radiation work; missing employment information) Weaknesses • No major weaknesses	Strengths • Semi-quantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job title, personnel listings, and expert opinion) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, CA death tapes and death 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 control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Did not include relevant covariates in a time-varying manner (*i.e.*, hydrazine exposure)	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses with workers ≥4 yrs of exposure) Weaknesses • No major weaknesses
Gun *et al.* (2006)	Employees of Australian Institute of Petroleum			B		Strengths • Appropriate study and comparison groups	Strengths • No major strengths Weaknesses	Strengths • Deaths identified from reliable sources (*i.e.*, NDI;	Strengths • Controlled for age, and sex • No missing data	Strengths • Exposure data collected prior to outcome

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
	member companies					• <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	• Indirect benzene exposure measurement (*i.e.*, survey interviews job codes ranked by industrial hygienists) • Qualitative exposure estimate (*i.e.*, ever exposed and job title) • Did not assess time-varying nature of exposure	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	Weaknesses • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Did not include relevant covariates in a time-varying manner	Weaknesses • No consideration of latency
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: age, sex, and race/ethnicity Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses by ≥10yrs of exposure) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									• Amount of missing data unknown	
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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • About 11% missing race; assumed white	Strengths • Exposure documented before outcome Weaknesses • Did not consider appropriate latency (employment for at least 1-yr)
Wilson *et al.* (2008)	Swedish general population	T	P			Strengths • Appropriate study and comparison groups • <2% excluded (*i.e.*, missing information) Weaknesses • No major weaknesses	Strengths • About 1% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported job titles from 1960 and 1970 National Population and Housing Censuses)	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, obesity, hypertension, genetic factors, family history of kidney cancer,	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Qualitative exposure estimate (*i.e.*, job title) • Did not assess time-varying nature of exposure		diabetes, alcohol consumption, or other potential occupational exposures • Did not consider relevant covariates in a time-varying manner (*i.e.*, smoking)	
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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Bahr *et al.* (2011)	Paducah Gaseous Diffusion Plant workers	T				Strengths • Appropriate study and comparison groups • No loss to follow-up; excluded <19%(*i.e.*, unusable data	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*,	Strengths • Cases identified using reliable sources (*i.e.*, KY Cancer Registry) • Assessed disease incidence • 51 yrs of follow-up	Strengths • Controlled for: age, sex, and race • No missing data Weaknesses • Did not control for or consider:	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						[<1%], few female deaths [18.2%]) Weaknesses • No major weaknesses	employment at facility and JEM) • Qualitative exposure estimate (*i.e.*, probability of exposure) • Did not assess time-varying nature of exposure	 Weaknesses • Not clear how vital status or death data were gathered	smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	
Calvert *et al.* (2011)	Dry cleaning workers		P			Strengths • Appropriate study and comparison groups • 5% loss to follow-up; <1% excluded (*i.e.*, missing age) Weaknesses • No major weaknesses	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment at shops using PCE) • Qualitative exposure estimate (*i.e.*, ever employment at shop) • Solvent history not available for approximately half of shops studied • 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 control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented prior to outcome Weaknesses • No consideration of latency
Lipworth *et al.* (2011)	Aircraft manufacturing workers	T	P			Strengths • Appropriate study and comparison groups • <2% lost to follow-up	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data	Strengths • Deaths identified using reliable sources (*i.e.*, CA Death Statistical Master File, NDI, SSA Death Master	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider:	Strengths • Exposure document before outcome • Appropriate consideration of latency (analyses by duration 10+ yrs,

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						Weaknesses • No major weaknesses	Weaknesses • Indirect chemical exposure measurement (*i.e.*, job codes/titles, facility files, walk-through visits, and employee interviews) • Did not assess time-varying nature	File, pension and other records, death certificates, and SSA Service to Epidemiologic Researchers and LexisNexis records) • 49 yrs of follow-up Weaknesses • Assessed mortality only	smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing race data unknown	and 5+ yrs of exposure) Weaknesses • No major weaknesses
Seldén and Ahlborg Jr. (2011)	Dry cleaning workers in Sweden		P			Strengths • Appropriate study and comparison groups • 2.8% loss to follow-up Weaknesses • 62.1% of companies excluded for not responding to questionnaire	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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure documented before outcome • Appropriate consideration of latency (sensitivity analysis included 15-yr lag) Weaknesses • No major weaknesses
Bove (2014a)	Marines & Navy Personnel at CL	T	P	B	V	Strengths • Appropriate study and comparison groups • <2% loss to follow-up	Strengths • Direct chemical exposure measurement (*i.e.*, measured in groundwater)	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, commercial tracing service, and NDI)	Strengths • Controlled for: age, sex, and race • Considered smoking using negative control diseases	Strengths • Exposure documented before outcome • Appropriate consideration of

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						<u>Weaknesses</u> • Number of participants excluded unknown	• Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data • Assessed time-varying nature of exposure <u>Weaknesses</u> • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	• 30 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Weaknesses</u> • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data is unknown	latency (*i.e.*, 10-yr lag) <u>Weaknesses</u> • No major weaknesses
Bove *et al.* (2014b)	Civilian employees at CL and CP	T	P	B	V	<u>Strengths</u> • Appropriate study and comparison groups • ≤2% loss to follow-up <u>Weaknesses</u> • Number of participants excluded unknown	<u>Strengths</u> • 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 <u>Weaknesses</u> • No direct chemical exposure measurement in	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, SSA, a commercial tracing service, and NDI/ NDI Plus) • 30 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age, sex, race, and occupation (as a proxy for other potential chemical exposures) • Considered smoking using negative control diseases <u>Weaknesses</u> • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer,	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10-yr lag) <u>Weaknesses</u> • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							individuals (*e.g.*, no water consumption information)		diabetes, or alcohol consumption • Did not include relevant covariates in a time-varying manner (*i.e.*, occupation) • Amount of missing data is unknown	
Carreón *et al.* (2014)	Workers at a chemical manufacturing plant				V	<u>Strengths</u> • Appropriate study and comparison groups • 2% loss to follow-up • <1% excluded <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, employment at facility) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, NDI, NDI Plus, and Florida Department of Health) • 48 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age, sex, and race/ethnicity <u>Weaknesses</u> • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • 54.2% missing race/ethnicity; assumed white	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silver *et al.* (2014)	Micro-electronics 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) • Number of subjects 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, conflicting data regarding work dates, facility location, department, and position (particularly for early yrs) that are not addressed • Did not consider 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 Weaknesses • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Race missing for 16% of cohort; assumed white	Strengths • Exposure documented before outcome • Appropriate consideration of latency (10-yr lag) Weaknesses • No major weaknesses
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)	Strengths • Deaths identified from company's research database (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, obesity, hypertension, genetic factors, family history of kidney cancer,	Strengths • Exposure documented before outcome • Appropriate consideration of latency (15- and 30-yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Qualitative exposure estimate (*i.e.*, any exposure) • Did not assess time-varying nature of exposure		diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data is unknown	
Buhagen *et al.* (2016)	Train repair and maintenance workers	T				Strengths • Appropriate study and comparison groups • <5% excluded (*i.e.*, missing or incorrect employment information) Weaknesses • Number of subjects 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, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • No major strengths Weaknesses • One subject diagnosed with kidney cancer before first exposure • 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)	Strengths • Deaths identified from 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, obesity, hypertension,	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Qualitative exposure estimate (*i.e.*, any exposure) • Did not assess time-varying nature of exposure		genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	
ATSDR (2018b)	Marines & Navy personnel and civilian employees at CL and CP	T	P	B	V	<u>Strengths</u> • Appropriate study and comparison groups <u>Weaknesses</u> • 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	<u>Strengths</u> • 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 <u>Weaknesses</u> • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	<u>Strengths</u> • Deaths validated using reliable sources (*i.e.*, medical records and death certificates) • Assessed disease incidence • 41 yrs of follow-up <u>Weaknesses</u> • Initial case identification relied on self-report	<u>Strengths</u> • Controlled for or considered: age, sex, race, smoking, alcohol consumption, and other potential occupational/chemical exposures <u>Weaknesses</u> • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, or diabetes • Did not consider relevant covariates in a time-varying manner (*i.e.*, smoking, alcohol consumption, occupational exposures) • >5% missing data for smoking, alcohol consumption, and	<u>Strengths</u> • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, "virtually all" participants developed cancer ≥10 yrs after being stationed or employed at CL) <u>Weaknesses</u> • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									other occupational exposures	
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 control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data is unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10- and 20-yr lag) Weaknesses • No major weaknesses
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)	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	Strengths • Controlled for: age, sex, race, and (for civilians) blue-collar work proxy for other occupational exposures • Considered quantitative bias from unmeasured smoking "negative control diseases" Weaknesses	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

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Did not assess time-varying nature of exposure	• No major weaknesses	• Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, 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	
Bove *et al.* (2024a)	Marines & Navy personnel and civilian workers at CL and CP	T	P	B	V	<u>Strengths</u> • Appropriate study and comparison groups • <1% loss to follow-up • No exclusions <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, assignment or employment at base) • Did not assess time-varying nature of exposure	<u>Strengths</u> • Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers and NDI) • 40 yrs of follow-up <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age, sex, race, and (for civilians) blue-collar work (proxy for other exposures) • Considered quantitative bias from unmeasured smoking "negative control diseases" <u>Weaknesses</u> • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer,	<u>Strengths</u> • Exposure documented before outcome <u>Weaknesses</u> • No consideration of latency (though, 75% of the deaths occurred >10 yrs after the water contamination ended)

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									diabetes, alcohol consumption, 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	
Case-Control Studies										
Asal *et al.* (1988)	Hospital cases in Tulsa and Oklahoma City, OK	T	P			Strengths • Appropriate case and control groups Weaknesses • Unknown participation rates in cases and controls	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported longest held job) • 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.*, hospital records) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, race, smoking, and obesity Weaknesses • Did not control for or consider: hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, and other potential occupational exposures • Amount of missing data is unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency
Brownson (1988)	MO residents included in the MO Cancer Registry	T				Strengths • Appropriate case selection Weaknesses	Strengths • No major strengths Weaknesses • Indirect chemical exposure	Strengths • Cases identified and validated using a reliable source (*i.e.*, MO Cancer Registry; histologically	Strengths • Controlled for: age, sex, race, smoking, and alcohol consumption	Strengths • Exposure considered prior to diagnosis Weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• Inappropriate control selection (*i.e.*, hospital-based) • Unknown number of exclusions	measurement (*i.e.*, self-reported longest held job) • Qualitative exposure estimate (*i.e.*, job title) • Amount of missing data unknown	confirmed by hospitals) • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Weaknesses</u> • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, or other potential occupational exposures • >5% missing data for smoking history and alcohol consumption	• No consideration of latency
Jensen *et al.* (1988)	General population of eastern Denmark	T				<u>Strengths</u> • Appropriate study group • High enrollment rates in cases and controls (99%) <u>Weaknesses</u> • Inappropriate comparison group (*i.e.*, hospital-based)	<u>Strengths</u> • No major strengths <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) • Qualitative exposure estimate (*i.e.*, job title) • Amount of missing data unknown	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, Danish Cancer Registry; histology [90%] or via combinations of X-ray, surgery, and urinary cytology [10%]) • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses •	<u>Strengths</u> • Controlled for: age, sex, and smoking <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data unknown	<u>Strengths</u> • Exposure considered prior to diagnosis <u>Weaknesses</u> • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Partanen *et al.* (1991)	Finnish general working population	T				Strengths • Appropriate case and control selection Weaknesses • Low participation rates in cases (69%) and controls (68%)	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self/proxy-reported occupational history) • Qualitative exposure estimate (*i.e.*, job title) • Potential for recall bias (*i.e.*, self/proxy-reported occupational history after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, Finnish Cancer Registry) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, and obesity • <5% missing data; imputed based on the mean values Weaknesses • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, considered occupational history with 10-yr lag) Weaknesses • No major weaknesses
Aschengrau *et al.* (1993)	General population of five Upper Cape towns, MA		P			Strengths • Appropriate case and control selection • High participation rate in cases (83%) • Characteristics of participants and non-participants were similar Weaknesses • Low participation rate in controls (74%)	Strengths • Quantitative 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)	Strengths • Cases identified and validated using reliable sources (*i.e.*, MA Cancer Registry; confirmed by medical professional) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age at diagnosis, sex, smoking, and occupational exposure to PCE, benzene, and other solvents Weaknesses • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors,	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (15-yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Amount of missing data unknown		family history of kidney cancer, diabetes, or alcohol consumption • Amount of missing data unknown	
McCredie and Stewart (1993)	General population of New South Wales, Australia	T	P	B		Strengths • Appropriate case selection Weaknesses • Inappropriate control selection (*i.e.*, non-compulsory electoral rolls) • Low participation rate among cases (68%) and controls (74%)	Strengths • No major strengths Weaknesses • Indirect exposure measurement (*i.e.*, self-reported occupational history) • 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 and validated using reliable sources (New South Wales Central Cancer Registry; confirmed with histopathology, fine needle aspiration cytology, CT, ultrasound, or contrast radiography) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, and, in fully adjusted renal pelvic cancer results, smoking • No missing data Weaknesses • Did not control for or consider: race/ethnicity, smoking (in all other results), obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency
Aupérin *et al.* (1994)	French general population	T	P			Strengths • Appropriate case selection • High participation rates for cases and controls (>99%) Weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported	Strengths • Cases identified using reliable sources (*i.e.*, hospital records) and histologically confirmed at hospital	Strengths • Controlled for: age, sex, smoking status, and BMI before diagnosis; excluded those with diabetes and alcoholic cirrhosis	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• Inappropriate control selection (*i.e.*, hospital-based)	occupational history) • Qualitative exposure estimate (*i.e.*, job title) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	• Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Weaknesses</u> • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, and other potential occupational exposures • Amount of missing data is unknown	
Greenland *et al.* (1994)	Workers at a transformer-assembly facility	T		B		<u>Strengths</u> • Appropriate case and control selection <u>Weaknesses</u> • About 40% of potential study population excluded (36% missing job history)	<u>Strengths</u> • <2% of person-yrs missing exposure level, assigned by imputation <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, work history records and JEM • Qualitative exposure estimate (*i.e.*, ever exposure)	<u>Strengths</u> • Deaths identified using reliable sources (*i.e.*, company pension office and death certificates); subset of cancer diagnoses were validated by medical professional <u>Weaknesses</u> • Assessed mortality only	<u>Strengths</u> • Controlled for: age, sex, and race • No missing data <u>Weaknesses</u> • Did not control for or consider: smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Exposure considered prior to outcome <u>Weaknesses</u> • Insufficient consideration of latency (2-yr lag)
Mellemgaard *et al.* (1994)	Danish general population	T	P			<u>Strengths</u> • Appropriate case and control selection	<u>Strengths</u> • No missing data <u>Weaknesses</u>	<u>Strengths</u> • Cases identified using a reliable source (*i.e.*, Danish Cancer Registry) and	<u>Strengths</u> • Controlled for: age, sex, smoking, and obesity	<u>Strengths</u> • Exposure considered prior to diagnosis

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						Weaknesses • Low participation rates among cases (76.4%) and controls (78.3%)	• Indirect chemical exposure measurement (*i.e.*, occupational history and JEM) • Qualitative exposure estimate (*i.e.*, job/industry title) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Weaknesses • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• Appropriate consideration of latency (10 yrs) Weaknesses • No major weaknesses
Delahunt *et al.* (1995)	New Zealand general population		P			Strengths • Appropriate case selection • Complete case and control ascertainment Weaknesses • Inappropriate comparison group (*i.e.*, non-urinary tract cancer controls)	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, current or most recent occupation listed on cancer-registry records) • Qualitative exposure estimate (*i.e.*, job title) • 14.8% of cases missing occupational code	Strengths • Cases identified using a reliable source (*i.e.*, New Zealand Cancer Registry) and histologically or cytologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for age, sex, and smoking status Weaknesses • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, and other potential occupational exposures • Amount of missing data is unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • Not consideration of latency
Mandel *et al.* (1995)	General populations of Australia,	T	P			Strengths	Strengths • Semiquantitative exposure estimate	Strengths • Cases identified using reliable	Strengths	Strengths

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
	Denmark, Germany, Sweden, and US					• Appropriate case and control selection Weaknesses • Low participation rates in cases (72.3%) and controls (74.7%)	(*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self/proxy-reported occupational history) • Amount of missing data unknown • Potential recall bias (*i.e.*, self/proxy-reported occupational history after diagnosis)	sources (*i.e.*, cancer registries and active surveillance of clinical and pathological departments) and were histologically or cytologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	• Controlled for: age, sex, smoking status, and obesity Weaknesses • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	• Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analyses with ≥4 yrs of exposure) Weaknesses • No major weaknesses
Schlehofer *et al.* (1995)	General population of the Rhein-Neckar-Odenwald area, Germany.	T				Strengths • Appropriate case and control selection • High enrollment rate in cases (84.5%) Weaknesses • Low participation rate in controls (75%)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and exposure to specific substances) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported occupational history	Strengths • Cases were identified using reliable sources (*i.e.*, urology departments) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, race, and smoking Weaknesses • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (must have worked or been exposed 5+ yrs) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							and exposure to substances)			
Gérin *et al.* (1998)	Canadian white males			B		Strengths • Appropriate case selection • High participation rate in cases (82%) Weaknesses • Inappropriate control selection (*i.e.*, non-compulsory electoral lists) • Low participation rate in controls (71%)	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 after diagnosis)	Strengths • Cases identified and validated 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: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, or alcohol consumption • Amount of missing data unknown	Strengths • Exposure considered prior to cancer diagnosis Weaknesses • No consideration of latency
Vamvakas *et al.* (1998)	Hospital cases in Germany	T				Strengths • Appropriate case selection • High enrollment rate in cases (85%) Weaknesses • Inappropriate control selection (*i.e.*, hospital-based, from accident ward) • Low enrollment rate in controls (~75%)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • <3% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self/proxy-reported occupational history	Strengths • Cases identified from a reliable source (*i.e.*, country hospital records) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, obesity, and hypertension Weaknesses • Did not control for or consider: race/ethnicity, genetic factors, family history of kidney cancer, diabetes, alcohol	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							and chemical exposures) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis) • Combined TCE and PCE exposure, however, only two subjects (both controls) were exposed to PCE		consumption, and other potential occupational exposures	
Dosemeci *et al.* (1999)	General population of MN, US	T	P			<u>Strengths</u> • Appropriate case and control selection • High participation rates in cases (87%) and controls (86%) <u>Weaknesses</u> • Excluded all cases who died (35%)	<u>Strengths</u> • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and JEM) • Qualitative exposure estimate (*i.e.*, ever exposure) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	<u>Strengths</u> • Cases identified using a reliable source (*i.e.*, MN Cancer Surveillance System) and were histologically confirmed • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Controlled for: age, sex, smoking, BMI, and hypertension status and/or use of diuretics and/or anti-hypertension drugs • No missing data <u>Weaknesses</u> • Did not control for or consider: genetic factors, family history of kidney cancer, diabetes, or other occupational exposures	<u>Strengths</u> • Exposure considered prior to diagnosis <u>Weaknesses</u> • No consideration of latency
Parent *et al.* (2000)	Male residents of Montreal, Canada	T	P			<u>Strengths</u> • Appropriate case selection <u>Weaknesses</u> • Some inappropriate control selection	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, hospital records) and were	<u>Strengths</u> • Controlled for: age, sex, smoking, and BMI <u>Weaknesses</u>	<u>Strengths</u> • Appropriate consideration of latency (*i.e.*, analyses with >10 yrs of employment

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						(*i.e.*, some analyses considered cancer controls) • Low participation rates in cases (78%) and controls (72%)	Weaknesses • Indirect chemical exposure measurement (*i.e.*, self/proxy-reported occupational history) • Potential for recall bias (*i.e.*, self/proxy-reported occupational history after diagnosis)	histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	• Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, or alcohol consumption • >5% missing BMI data	for metal fabricating and machining workers) Weaknesses • Unclear if occupational history included time after diagnosis
Pesch *et al.* (2000a)	German general population	T	P	B		Strengths • Appropriate case and control selection • High participation rate in cases (84-95% depending on region) Weaknesses • Low participation rate in controls (63-75%) • Case and control participation rates differed >15%	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and JEM) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths • Cases identified and validated using reliable sources (*i.e.*, hospital records, histological confirmation, and sonography) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, and smoking Weaknesses • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, 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
Mattioli *et al.* (2002)	Hospital cases in Bologna	T		B		Strengths • Appropriate case selection	Strengths • No major strengths	Strengths • Cases identified using a reliable	Strengths • Controlled for: age, sex, smoking,	Strengths • No major strengths

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
	and its province, Italy					<u>Weaknesses</u> • Inappropriate comparison group (*i.e.*, hospital-based) • Low participation rate in both cases and controls (*i.e.*, 32.4%)	<u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported job/occupational history) • Qualitative exposure estimate (*i.e.*, job title) • Amount of missing data unknown	source (*i.e.*, hospital records) and histologically confirmed • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	obesity, and alcohol consumption <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, or other potential occupational exposures • Amount of missing data is unknown	<u>Weaknesses</u> • Unclear if occupational history considered after diagnosis • No consideration of latency
Brüning *et al.* (2003)	General population of Western Germany	T	P	B		<u>Strengths</u> • Appropriate case selection • High enrollment rate in cases (82.7%) <u>Weaknesses</u> • Inappropriate control selection (*i.e.*, hospital-based) • Unknown enrollment rate in controls	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • <1% missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self/proxy-reported occupational history and JEM) • Potential for recall bias (*i.e.*, self/proxy-reported occupational history after diagnosis)	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, hospital registries) and histologically confirmed • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Controlled for: age, sex, and smoking status • <1% missing data for smoking status <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, and other potential	<u>Strengths</u> • Appropriate consideration of latency (*i.e.*, analyses by 5-10,10-20, and 20+ yrs since first/last exposure) <u>Weaknesses</u> • Unclear if occupational history included time after diagnosis

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									occupational exposures	
Zhang *et al.* (2004)	Iowa general population	T				Strengths • Appropriate case and control selection • High enrollment rate in cases (88%) and controls (82%) Weaknesses • No major weaknesses	Strengths • Semi-quantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported job title/occupational history) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, State Health Registry) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, BMI, hypertension, and first-degree relative with kidney cancer Weaknesses • Did not control for or consider: race/ethnicity, genetic factors, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analyses with ≥10 yrs of employment) Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Charbotel *et al.* (2006)	General population of the Arve Valley, France	T				Strengths • Appropriate case selection • Assessed potential selection bias by collecting data on non-participants Weaknesses • Inappropriate control selection (*i.e.*, recruited from urologists' offices) • Low participation rates in cases (74%) and controls (78%)	Strengths • Direct chemical exposure assessment (*i.e.*, self/proxy-reported occupational history and task-exposure matrix linked with U-TCA or air-monitoring data) • Semiquantitative exposure estimate (*i.e.*, considered duration, intensity, and peaks) Weaknesses • Amount of missing data unknown	Strengths • Cases identified using reliable sources (*i.e.*, various medical office records) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, and BMI • 2% missing data for smoking or BMI Weaknesses • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, and other potential occupational exposures	Strengths • No major strengths Weaknesses • Unclear if occupational history considered after diagnosis • No consideration of latency

Study	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%)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self/proxy-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, smoking, and alcohol consumption Weaknesses • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, or other potential occupational exposures • Amount of missing data is unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analyses with 5+ yrs of employment) Weaknesses • No major weaknesses
Moore *et al.* (2010)	Hospital cases from the Czech Republic, Poland, Romania, and Russia	T				Strengths • Appropriate case selection Weaknesses • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered, duration, frequency and intensity) Weaknesses	Strengths • Cases identified using reliable sources (*i.e.*, hospital records) and histologically confirmed • Assessed disease incidence	Strengths • Controlled for or considered: age, sex, smoking, obesity, and hypertension Weaknesses	Strengths • Appropriate consideration of latency (20-yr lag) Weaknesses • Unclear if occupational history

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
						• Unknown participation rates in cases and controls	• Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and assigned exposure by industrial hygienist)	<u>Weaknesses</u> • No major weaknesses	• Did not control for or consider: race/ethnicity, genetic factors, family history, diabetes, alcohol consumption, or other potential occupational exposures • Amount of missing data is unknown	considered after diagnosis
Karami *et al.* (2012b)	Caucasian and African American general populations of Chicago, IL and Detroit, MI		P			<u>Strengths</u> • Appropriate case and control selection <u>Weaknesses</u> • Low participation rates in cases (77.5%) and controls (54.4%) • Case and control participation rates differed >15%	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history)	<u>Strengths</u> • Cases identified using reliable sources (*i.e.*, Metropolitan Detroit Cancer Surveillance System and pathology reports in Chicago) • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Controlled for: age, sex, race, smoking, BMI, hypertension, family history of cancer, and hypertension • About 1% missing data for BMI and hypertension; no missing data for other variables <u>Weaknesses</u> • Did not control for or consider: genetic factors, diabetes, alcohol consumption, or other potential occupational exposures	<u>Strengths</u> • Appropriate consideration of duration (analyses by 5+ yrs of employment) <u>Weaknesses</u> • Unclear if occupational history considered after diagnosis
Christensen *et al.* (2013)	Male Canadian	T	P			<u>Strengths</u> • Appropriate case selection	<u>Strengths</u> • Semiquantitative exposure estimate	<u>Strengths</u> • Cases identified using a reliable	<u>Strengths</u> • Controlled for: age, sex, ethnicity,	<u>Strengths</u>

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
	citizens living in Montreal					• High participation rate in cases (82%) Weaknesses • Inappropriate control selection (non-compulsory electoral lists) • Low participation rate in controls (72%)	(*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)	source (*i.e.*, hospital records) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	smoking, and alcohol consumption Weaknesses • Did not control for or consider: obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, and other potential occupational exposures • Amount of missing data is unknown	• Appropriate consideration of latency (5-yr lag) Weaknesses • Unclear if exposure period included time after diagnosis
Vlaanderen *et al.* (2013)	General population in Nordic Countries	T	P			Strengths • Appropriate case and control selection • Nested case-control design; no issues with participation/enrollment Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported census data and JEMs) • Occupations and industries based on decennial censuses	Strengths • Cases identified using reliable sources (*i.e.*, national population and cancer registries) • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, alcohol consumption, or other potential occupational exposures	Strengths • Exposure considered prior to diagnosis • Considered appropriate latency (5-, 10-, and 20-yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Purdue *et al.* (2017)	General populations of Detroit MI, and Chicago, IL	T	P			Strengths • Appropriate case and control selection Weaknesses • Low participation rates among cases (77%) and controls (54%) • Case and control participation rates differed >15%	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and chemical exposure) • Amount of missing data unknown	Strengths • Cases identified using a reliable source (*i.e.*, Metropolitan Detroit Cancer Surveillance System) and histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, race, smoking, obesity, and hypertension • <2% missing obesity or hypertension data; no missing data for other variables Weaknesses • Did not control for or consider: genetic factors, family history of kidney cancer, diabetes, alcohol consumption or other potential occupational exposures	Strengths • Appropriate consideration of latency (5- and 15-yr lags) Weaknesses • Unclear if occupational history considered after diagnosis
Michalek *et al.* (2019)	General populations of Finland, Iceland, and Sweden	T				Strengths • Appropriate case selection • Participation in censuses was mandatory Weaknesses • Inappropriate control selection; participants were allowed to have a history of non-kidney cancer	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (self-reported occupational history 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 occupational exposures (*i.e.*, alicyclic hydrocarbons, asbestos, chlorinated hydrocarbon solvents, diesel engine exhaust, nickel, lead, perceived physical	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (0-, 10-, and 20-yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
							• Exposure based on decennial censuses		workload, quartz dust, ultraviolet radiation, welding fumes, and wood dust) • No missing data <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, smoking, obesity, hypertension, genetic factors, family history of kidney cancer, diabetes, and alcohol consumption	
Purdue *et al.* (2021)	Hospital cases from the Czech Republic, Poland, Romania, and Russia	T				<u>Strengths</u> • Appropriate case selection • High participation rates among cases and controls (≥90%) <u>Weaknesses</u> • Inappropriate control selection (*i.e.*, hospital-based)	<u>Strengths</u> • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) <u>Weaknesses</u> • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and industrial hygienist review) • About 20% missing exposure data	<u>Strengths</u> • Cases identified using a reliable source (*i.e.*, hospital records) and histologically confirmed • Assessed disease incidence <u>Weaknesses</u> • No major weaknesses	<u>Strengths</u> • Controlled for: age, sex, smoking, obesity, hypertension, and family history of kidney cancer • <1% missing smoking and hypertension data; no missing data for other variables <u>Weaknesses</u> • Did not control for or consider: race/ethnicity, diabetes, alcohol	<u>Strengths</u> • No major strengths <u>Weaknesses</u> • Unclear if occupational history considered after diagnosis • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									consumption, or other potential occupational exposures	
Andrew *et al.* (2022)	Individuals in the Dartmouth-Hitchcock Health System living in New Hampshire	T				Strengths • Appropriate case and control selection Weaknesses • Unknown participation rates in cases and controls	Strengths • Direct chemical exposure measurement (*i.e.*, groundwater contamination modeling based on measured groundwater TCE amounts) • Semiquantitative exposure estimate (*i.e.*, considered and intensity) Weaknesses • No direct chemical exposure measurement in individuals (*i.e.*, no water consumption information) • 50% missing residential addresses for ≥3 of prior 15 yrs	Strengths • Cases identified using a reliable source (*i.e.*, Dartmouth Hitchcock Health System) and 90% histologically confirmed • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, BMI, diabetes, and alcohol consumption Weaknesses • Did not control for or consider: race/ethnicity, hypertension, genetic factors, family history of kidney cancer, or other potential occupational exposures • Amount of missing data is unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 15-yr lag) Weaknesses • No major weaknesses

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Benzene; BMI = Body Mass Index; CA = California; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; CT = Computed Tomography; DHSS = Department of Health and Social Security; DMF = Death Master File; DMV = Department of Motor Vehicles; FIOH = Finnish Institute of Occupational Health; HCFA = Health Care Financing Administration; HIPPA = Health Insurance Portability and Accountability Act; HR = Human Resources; IL = Illinois; IRS = Internal Revenue Service; JEM = Job Exposure Matrix; KY = Kentucky; MA = Massachusetts; MI = Michigan; MN = Minnesota; MO = Missouri; NDI = National Death Index; OK = Oklahoma; ONS = Office of National Statistics; P = Perchloroethylene; PAH = Polycyclic Aromatic Hydrocarbon; PBI = Pension Benefits Information; PCE = Perchloroethylene; RR = Relative Risk; 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; V = Vinyl Chloride; VA = Veterans Administration; yrs = Years.

Attachment D

TCE Epidemiology Studies

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Table D.5 TCE and Kidney Cancer Meta-Analyses and Pooled Study Results

Table D.1 TCE and Kidney Cancer Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Garabrant *et al.* (1988)	US	Aircraft manufacturing workers	B	–	14,067	1958-1982	Personnel records	Mort	Kidney	SSA, California DMV, credit records, death certificates, California Death Tapes	1958-1982
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Kidney	Death certificate	1942-1980
Sinks *et al.* (1992)	US	Paperboard printing workers	B	Median = 44.6 (range: 19.4-83.1)	2,050	1957-1988	Work history and Material Safety Data Sheets	Inc & Mort	RCC	SSA and death certificates (mortality) and company interviews and medical records, death certificates, and SEER and Georgia State Tumor registries (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	Kidney	Swedish cause of death and cancer registers	1955-1986 mortality, 1958-1987 incidence
Anttila *et al.* (1995)	Finland	FIOH workers	B	–	3,089	1965-1982	U-TCA	Inc	Kidney	Finnish Cancer Registry and Central Statistical Office of Finland	1967-1992
Henschler *et al.* (1995a)	Germany	Cardboard factory workers	M	28-89	169	1956-1975	Job history	Inc & Mort	Kidney	Medical records, histopathological examination	1957-1992

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Morgan *et al.* (1998)	US	Aircraft manufacturing workers	B	–	20,508 (TCE-exposed sub-cohort: 4,733)	1950-1985	JEM	Mort	Kidney	SSA and NDI	1950-1993
Ritz (1999)	US	Uranium-processing workers	M	30.5[a]	3,814	1951-1989	JEM	Mort	Kidney	SSA and NDI	1951-1989
Hansen *et al.* (2001)	Demark	TCE exposed workers	B	–	803	1964-1989	U-TCA & air-TCE	Inc	Kidney	Danish Cancer Registry	1968-1996
Travier *et al.* (2002)	Sweden	Dry-cleaning workers	B	–	3,742	1960/1970 census	Census JEM	Inc	Kidney	CERIII	1971-1989
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	39.25[b]	86,868	1973-1997	Employment in the factory	Mort	Kidney and other unspecified urinary organs	National Mortality Database	1985-1997
Raaschou-Nielsen *et al.* (2003)	Denmark	Blue-collar workers at companies using TCE	B	–	40,049	1964-1997	Employed at TCE-using companies and JEM	Inc	Kidney; renal parenchyma; renal pelvis/ureter	Danish cancer registry	1968-1997
Ji *et al.* (2005)	Sweden	Working Swedish population	B	–	M: 1,644,958 F: 1,154,091	1960/1970 census	Occupation listed on census	Inc	Renal parenchyma[c]	Swedish Family-Cancer Database	1961-2000
Zhao *et al.* (2005)	US	Aerospace workers	M	68.7 (mortality)[b]; 68.6 (incidence)[b]	Mortality: 6,044 Incidence: 5,049	1950-1993	JEM	Inc & Mort	Kidney	SSA, vital statistics, NDI, and state cancer registries	1950-2001 (mortality); 1988-2000 (incidence)
Boice *et al.* (2006)	US	Aerospace workers	M	–	8,372	1948-1999	JEM	Mort	Kidney	California death tapes, NDI, death certificates	1948-1999

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Sung *et al.* (2007)	Taiwan	Electronics factory workers	F	–	63,982	1973-1992	Employment records from labor insurance database	Inc	Kidney and other urinary organs	Taiwan National Cancer Registry	1979-2001
Radican *et al.* (2008) [Blair *et al.*, 1998; Spirtas *et al.*, 1991]	US	Aircraft maintenance employees	B	–	14,455	1952-1956	JEM	Mort	Kidney	NDI Plus	1979-2000
Wilson *et al.* (2008)	Sweden	Employed Swedish Residents	B	–	4,197,684	1960/1970 census	JEM	Inc	Renal pelvis	CERIII	1971-1989
Pukkala *et al.* (2009) [Andersen *et al.*, 1999; Lynge and Thygesen, 1990]	Denmark, Finland, Iceland, Norway, and Sweden	General population	B	30-64[d]	≈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	Kidney	National registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004
Bahr *et al.* (2011)	US	Paducah Gaseous Diffusion Plant	M	–	5,535	1952-2003	JEM	Inc	Kidney	Kentucky Cancer Registry and death certificates	1952-2003
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	45,318 (5,443 exposed to TCE)	–	JEM	Mort	Kidney	California Death Statistical Master File, NDI, SSA, death certificates, and company records	1960-2008

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Bove *et al.* (2014a)	US	Marines and Navy 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	Kidney	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[e] CP: 34-60[e]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Kidney	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics facility workers	B	25.7-28.7[a]	34,494	1969-2001	Employment at the facility	Mort	Kidney	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	Kidney	Norwegian cancer registry	1960-2010
ATSDR (2018b)[f]	US	Marines and Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[g] Civilian Employees CL: 60-64[g] CP: ≥65[g]	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 (Marine and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Kidney	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Notes (continued on next page):

ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; F = Females; FIOH = Finnish Institute of Occupational Health; Inc = Incidence; IRS = Internal Revenue Service; JEM = Job Exposure Matrix; M = Males; Mort = Mortality; NDI = National Death Index; NRCD = National Registry of the Cause of Death; RCC = Renal Cell Carcinoma; SSA = Social Security Administration; TCE = Trichloroethylene; U-TCA = Urinary Trichloroacetic Acid; US = United States; Yr(s) = Year(s).
– = 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-upChang *et al*., 2003; Zhao *et al*., 2005).
(c) Ji *et al*. (2005) also reports results for total kidney cancer and renal pelvis cancer, however, these outcomes were better covered by Pukkala *et al*. (2009) and Wilson *et al*. (2008), respectively.
(d) Age at initial census (Pukkala *et al*., 2009).
(e) Median age from start to end of follow-up (Bove *et al*., 2014a,b).
(f) 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, 2018b).
(g) Median age at survey or death (ATSDR, 2018b).

Table D.2 TCE and Kidney 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	12	12.8	0.93 (0.48-1.64)	–	Age, sex, race, and calendar year
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	3	3	1.06 (0.22-3.10)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	1.03 (0.21-3.01)		
Sinks *et al.* (1992)[b]	US general population	Mort	SMR	Overall	1	0.7	1.4 (0.0-7.7)	–	Age, sex, and calendar time
	Atlanta-SEER registry (1973-1977)	Inc	SIR	All white male employees	6	1.6	**3.7 (1.4-8.1)**	–	Age
Axelson *et al.* (1994)	Sweden general population	Inc	SIR	Overall	6	5.2	1.16 (0.42-2.52)	--	Age, sex, and calendar yr
Anttila *et al.* (1995)	Finland general population	Inc	SIR	Overall	6	–	0.87 (0.32-1.89)	–	Sex, age, and calendar yr
				Yrs of Follow-Up					
				0-9	1	–	0.53 (0.01-2.95)	–	
				10-19	5	–	1.39 (0.45-3.24)		
				20+	0	1.48	–		
Henschler *et al.* (1995a)	Cancer registry of Denmark	Inc	SIR	Overall exposed	5	0.6	**7.97 (2.59-8.59)**	–	Age and sex
	Cancer registry of the former German Democratic Republic		SIR	Overall exposed	5	–	**9.66 (3.14-22.55)**	–	
	Unexposed workers		OR	Overall exposed	5	–	–	**0.014**	
	Local population	Mort	SMR	Overall exposed	2	0.6	3.28 (0.40-11.84)	–	
Morgan *et al.* (1998)	US general population	Mort	SMR	All workers	32	28.0	1.14 (0.78-1.61)	–	Age
				TCE-Exposed Sub-Cohort					
				All workers	8	6.1	1.32 (0.57-2.60)	–	
				Low cumulative exposure	1	2.13	0.47 (0.01-2.62)	–	
				High cumulative exposure	7	3.94	1.78 (0.72-3.66)		
	Low & no exposure		RR	Peak: medium & high exposure	8	–	1.89 (0.85-4.23)	–	Age and sex

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
	No exposure			Low cumulative	1	–	0.31 (0.04-2.36)	–	
				High cumulative	7	–	1.59 (0.68-3.71)		
Ritz (1999)	US general population	Mort	SMR	Overall	5	7.72	0.65 (0.21-1.51)	–	Age, sex (by design), race (by design), and calendar yr
Hansen *et al.* (2001)	Danish general population	Inc	SIR	Overall	4	–	1.1 (0.3-2.7)	–	Age, sex, and calendar yr
				Males	3	3.3	0.9 (0.2-2.6)	–	
				Females	1	0.4	2.4 (0.03-14)	–	
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**Persons Classified with Relevant Occupational or Industrial Code at Time of One or Both Censuses**					Sex, age, calendar period, geographic region, and urban setting
				Overall	121	–	1.11 (0.93-1.33)	–	
				Persons Classified with Relevant Occupational or Industrial Code at Time of Both Censuses					
				Overall	14	–	1.20 (0.71-2.02)	–	
				Female	11	–	1.59 (0.88-2.87)	0.12	
				Male	3	–	0.62 (0.20-1.93)		
Chang *et al.* (2003)	Taiwan general population	Mort	SMR	Male	0	1.31	–	–	Age, calendar yr, and sex
				Female	3	2.55	1.18 (0.24-3.44)		
				Duration of Employment (Yrs)					
				≤1	1	1.61	0.62	>0.05	
				>1 to 5	2	0.65	3.08		
				>5	0	0.28	–		
				Calendar-Yr Interval					
				1985-1990	0	0.65	–	>0.05	
				1991-1997	3	1.90	1.58		

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
Raaschou-Nielsen *et al.* (2003)[c]	Danish general population	Inc	SIR	**Overall Kidney Cancer**					Sex, age, and calendar yr
				Men	93	77.1	1.2 (0.97-1.48)	–	
				Women	10	8.7	1.2 (0.55-2.11)		
				Overall Renal Parenchyma					
				Men	68	57.1	1.2 (0.93-1.51)	–	
				Women	8	6.5	1.2 (0.53-2.44)		
				Overall Renal Pelvis, Ureter					
				Men	25	20.1	1.2 (0.81-1.84)	–	
				Women	2	2.2	0.9 (0.10-3.27)		
				RCC in Sub-Cohort with Expected Higher TCE Exposure Levels[d], Males and Females Combined					
				Overall	53	–	1.4 (1.0-1.8)	–	
				Lag time (yrs)					
				0-9	6	–	0.9 (0.3-1.8)	–	
				10-19	22	–	1.5 (0.9-2.2)		
				≥20	25	–	1.6 (1.0-2.3)		
				Duration of employment (yrs)					
				1-4.9	23	–	1.1 (0.7-1.7)	–	
				≥5	30	–	**1.7 (1.1-2.4)**		
				Yr of first employment					
				Before 1970	41	–	**1.9 (1.4-2.6)**	–	
				1970-1979	12	–	0.7 (0.4-1.2)		
Ji *et al.* (2005)	Workers in other occupations in Sweden	Inc	SIR	**Mechanics, Iron and Metalware Workers**					Age, sex, calendar period, and SES
				Males in 1960 census	1,016	–	1.03 (0.97-1.10)	–	
				Females in 1970 census	47	–	0.94 (0.69-1.22)		
				Electronics Workers					
				Males in 1960 census	304	–	0.97 (0.86-1.08)	–	
				Females in 1970 census	23	–	0.96 (0.61-1.40)		
Zhao *et al.* (2005)	Low TCE exposure	Mort	RR	**Cumulative TCE Exposure, No Exposure Lag**					Time since first employment, SES, and age at event
				Low	7	–	Ref	0.307	
				Medium	7	–	1.43 (0.49-4.16)		
				High TCE	3	–	2.03 (0.50-8.32)		
		Inc		Low	6	–	Ref	**0.023**	
				Medium	6	–	1.87 (0.56-6.20)		
				High	4	–	**4.90 (1.23-19.6)**		

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
		Mort		**Cumulative TCE Exposure, Adjusting for Other Carcinogens**					Time since first employment, SES, age at event, and other measured carcinogens (*i.e.*, hydrazine, PAHs, mineral oils)
				No exposure lag					
				Low	7	–	Ref	0.933	
				Medium	7	–	0.85 (0.15-4.93)		
				High	3	–	0.96 (0.09-9.91)		
		Inc		Low	6	–	Ref	0.103	
				Medium	6	–	1.26 (0.26-6.14)		
				High	4	–	7.71 (0.65-91.4)		
		Mort		*20-yr exposure lag*					
				Low	10	–	Ref	0.635	
				Medium	6	–	1.69 (0.29-9.70)		
				High	1	–	1.82 (0.09-38.6)		
		Inc		Low	6	–	Ref	0.120	
				Medium	7	–	1.19 (0.22-6.40)		
				High	3	–	7.40 (0.47-116)		

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
Boice *et al.* (2006)	California general population	Mort	SMR	Overall	21	–	1.15	–	Race, age, sex, and calendar yr of death
				Male Test Stand Mechanics					Race, age, sex (by design), and calendar yr of death
				Overall	7	3.2	2.22 (0.89-4.57)	–	
	Rocketdyne workers who were not test stand mechanics or monitored for radiation		RR	*Yrs of potential TCE exposure (engine flush)[d]*					Yr of birth and yr of hire
				0	3	–	1.21 (0.33-4.35)	0.59	
				<4	1	–	2.51 (0.27-23.5)		
				≥4	3	–	3.13 (0.74-13.2)		
				Yrs worked at SSFL					Pay type, yr of birth, yr of hire, and sex
				<5	15	–	1.47 (0.82-2.63)	0.68	
				5-9	2	–	0.64 (0.16-2.64)		
				≥10	4	–	1.11 (0.40-3.13)		
Sung *et al.* (2007)	Taiwanese general population	Inc	SIR	All female workers	15	13.6	1.10 (0.62-1.82)	–	Age and calendar yr
Radican *et al.* (2008)	Unexposed workers	Mort	HR	Overall	18	–	1.18 (0.47-2.94)	–	Age, sex, race, and calendar time
				Cumulative TCE Exposure Score					
				Males					
				Low, intermittent	15	–	1.58 (0.52-4.76)	–	
				Low, continuous	11	–	1.79 (0.57-5.62)		
				Peak, infrequent	2	–	1.04 (0.19-5.70)		
				Peak, frequent	6	–	1.11 (0.31-3.96)		
				Females					
				Low, intermittent	0	–	–	–	
				Low, continuous	0	–	–		
				Peak, infrequent	0	–	–		
				Peak, frequent	2	–	1.50 (0.24-9.40)		
Wilson *et al.* (2008)	Swedish employed population	Inc	SIR	**Machine and Electronics Industry**					Age, sex, and calendar yr
				Female	18	–	**1.75 (1.04-2.76)**	–	
				Male	120	–	**1.30 (1.08-1.55)**		
				Occupation					
				Females					
				Shop and construction metal worker	8	–	1.66 (0.71-3.26)	–	

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
				Shop and metal industry work, other	7	–	2.32 (0.93-4.78)		
				Laundry workers	8	-	1.45 (0.63-2.86)		
				Males					
				Shop and construction metal worker	143	–	1.19 (1.00-1.40)	–	
				Machine assembler	17	–	1.62 (0.94-2.59)		
				Metal plating worker	4	–	2.70 (0.73-6.92)		
				Shop and metal industry work, other	14	–	0.98 (0.54-1.65)		
				Laundry workers	3	-	1.07 (0.21-3.12)		
Pukkala *et al.* (2009)	Employed population in Denmark, Finland, Iceland, Norway, and Sweden	Inc	SIR	**Kidney Cancer**					Country, sex, age, and 5-yr calendar periods
				Men					
				Mechanics	3,669	–	**1.06 (1.02-1.09)**	–	
				Electrical Workers	1,289	–	1.02 (0.97-1.08)		
				Painters	671	–	0.96 (0.89-1.04)		
				Printers	395	–	1.01 (0.92-1.12)		
				Women					
				Mechanics	170	–	1.13 (0.97-1.31)	–	
				Electrical Workers	114	–	1.07 (0.89-1.28)		
				Painters	8	–	0.61 (0.26-1.21)		
				Printers	98	–	1.06 (0.86-1.29)		
				Cancer of the Renal Pelvis					
				Male Printers	–	–	**1.39 (1.09-1.74)**	–	
Bahr *et al.* (2011)	US general population	Inc	SRR	**TCE Exposure Category**					Age, sex, and race
				0	0	–	–	–	
				1	0	–	–		
				2	0	–	–		
				3	0	–	–		
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	California general population (white workers), US general population (non-white workers)	Mort	SMR	Factory workers exposed to TCE	16	24.2	0.66 (0.38-1.07)	–	Race, age, calendar yr, and sex

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
	Unexposed factory workers		RR	**Duration of Exposure (yrs)**					Date of birth, date of hire, date of termination, sex, and race
				0	33	–	Ref.	>0.20	
				<1	6	–	0.52 (0.21-1.30)		
				1-4	3	–	0.42 (0.13-1.42)		
				≥5	6	–	0.85 (0.33-2.19)		
Bove *et al.* (2014a)	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)[e]	23	–	0.95 (0.48-1.86)	–	
				Medium/high (>3,100-8,585)[e]	19		1.50 (0.91-2.49)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[f]			Low (>1-3,100)	11		1.54 (0.65-3.61)		
				Medium (>3,100-7,700)	8		1.21 (0.47-11.46)		
				High (>7,700-39,745)	11		1.52 (0.64-3.61)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Maximum cumulative exposure level with 10-yr lag[f]					
				≥Median	7	0	∞	–	
Silver *et al.* (2014)	Workers of full risk set	Mort	HR	Cumulative TCE exposure	–	–	1.24 (0.87-1.77)	–	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	37	–	1.22 (0.86-1.68)	–	
				Females	6	–	1.07 (0.39-2.34)		
				Salaried Employees					
				Males	13	–	0.60 (0.32-1.03)	–	
				Females	0	–	0.00 (0.00-7.78)		
Buhagen *et al.* (2016)	Norway general population	Inc	SIR	Overall	13	7.5	1.7 (1.0-3.0)	–	Age, and calendar yr
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[g,h]					
				Low (<110)	82	–	0.90 (0.56-1.45)	–	
				Medium (110-<11,030)	86		1.33 (0.84-2.13)		
				High (≥11,030)	24		1.42 (0.78-2.58)		
				Medium (110-<11,030)	86		**1.45 (1.05-2.00)**		

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
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)[i]			High (≥11,030)	24		1.55 (0.95-2.54)		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[g,j]					
				Low (<10,868)	3	–	0.34 (0.09-1.25)	–	
				Medium (10,868-<50,563)	8		1.80 (0.68-4.76)		
				High (≥50,563)	9		**13.92 (5.09-38.10)**		
	CL civilian employees with low exposure (<10,868 µg/L-mos)[i]			Medium (10,868-<50,563)	8		**5.34 (1.38-20.6)**		
				High (≥50,563)	9		41.54 (0.30-76.10)		

Notes:

ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; HRR = Hazard Rate Ratio; Inc = Incidence; Mos = Months; Mort = Mortality; NR = None to Report; NYC = New York City; OR = Odds Ratio; PAHs = Polycyclic Aromatic Hydrocarbons; PCE = Tetrachloroethylene; Ref = Reference; RR = Relative Risk; RCC = Renal Cell Carcinoma; SES = Socioeconomic Status; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SRR = Standardized Rate Ratio; SSFL = Santa Susana Field Laboratory; TVOC = Total Volatile Organic Compound; 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) The authors also conducted a nested case-control study for RCC within the cohort and presented results based on employment in a specific department in a paperboard printing manufacturing plant for five or more years. However, the reported ORs were unstable with the effect estimates ranging from 0 to infinity (Sinks *et al.*, 1992).

(c) Raaschou-Nielsen *et al.* (2003) also assessed risk of RCC and renal pelvis stratified by sex. None of the results were statistically significant except for RCC and duration of employment 5+ years for men.

(d) Expected higher exposure levels based on the criteria that participants had at ≥1-year duration of employment and year of first employment was before 1980 (Raaschou-Nielsen *et al.*, 2003).

(e) 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.*, 2014a). I report the values consistent with the text definition.

(f) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al.*, 2014a,b).

(g) 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, 2018b).
(h) 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).
(i) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.
(j) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table D.3 TCE and Kidney 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	
Asal *et al.* (1988)	US	Inc	RCC	1981-1984	B	60	315	Hospitals	Hospital: 313 Population: 336	Hospitals and random-digit dialing	Self-reported occupation history
Brownson (1988)	US	Inc	RCC	1984-1986	B	≥20	326	State cancer registry	978	State cancer registry	Self-reported longest held job
Jensen *et al.* (1988)	Denmark	Inc	Renal pelvis & ureter	1979-1982	B	<80	96	Hospitals	294	Hospitals	Self-reported occupation and occupational exposures
Partanen *et al.* (1991)	Finland	Inc	RCC	1977-1978	B	26-95	338	Finnish Cancer Registry	338	Population register	Self-reported occupational history
McCredie and Stewart (1993)	Australia	Inc	RCC and CaRP	1989-1990	B	20-79	RCC: 489; CaRP: 147	New South Wales Central Cancer Registry	523	New South Wales electoral rolls	Self-reported occupational history
Aupérin *et al.* (1994)	France	Inc	RCC	1987-1991	B	–	196	Hospitals	347	Hospitals	Self-reported occupational history and job durations
Greenland *et al.* (1994)[h]	US	Mort	Kidney	1969-1984	M	21-90	512	Employee pension records	1,202	Workers at same transformer-manufacturing facility	Job history records and JEM
Mellemgaard *et al.* (1994)	Denmark	Inc	RCC	1989-1992	B	20-79	365	National cancer registry, and pathology department files	396	Central population registry	Self-reported employment in occupations and industries, and chemical exposures

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Delahunt *et al.* (1995)	New Zealand	Inc	RCC	1978-1986	M	≥20	710	New Zealand Cancer Registry	12,756	New Zealand Cancer registry	Cancer registry records, current or most recent occupation at registration
Mandel *et al.* (1995)	Australia US Denmark Sweden Germany	Inc	RCC	1989-1991	M	20-79	1,732	National cancer registries and Clinical surveillance systems	2,309	Population-based electoral lists, Health Care Financing Administration lists, and RDD Population registry Residential lists	Occupation, industry and exposures, face-to-face interviews
Schlehofer *et al.* (1995)	Germany	Inc	RCC	1989-1991	B	20-75	277	Urological and surgical clinics	286	Population register	Self-reported occupational information
Vamvakas *et al.* (1998)	Germany	Inc	RCC	1987-1992	B	Cases: $\bar{x}$ = 62 Controls: $\bar{x}$ = 51	58	Hospital records	84	Hospital records	Self-reported occupational information
Dosemeci *et al.* (1999)	US	Inc	RCC	1988-1990	B	20-85	438	Minnesota Cancer Surveillance System	687	Random digit dialing and HCFA	Self-reported occupational history and JEM

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Parent *et al.* (2000)	Canada	Inc	RCC	1979-1985	M	35-70	142	Hospital	1,900 (cancer controls) and 533 population controls	Hospital (cancer controls) and random digit dialing (population controls)	Self-reported occupational information
Pesch *et al.* (2000a)	Germany	Inc	RCC	1991-1995	B	Median: 61-67	935	Population-based enrollment, hospitals in the study areas	4,298	Population-based enrollment, local residency registries	Interviews, self-reported job history, JEM
Mattioli *et al.* (2002)	Italy	Inc	RCC	1987-1994	M	Median: 60-69	150	Hospital records	150	Hospital records	Self-reported occupational history
Brüning *et al.* (2003)	Germany	Inc	Kidney	1992-2000	B	Cases: median = 68 Controls: median = 66	134	Hospital records	401	Hospital records	Self-reported occupational history linked to JEM and self-assessed exposure to TCE
Zhang *et al.* (2004)	US	Inc	RCC	1985-1987	B	40-85	406	State registry	2,434	DMV records (if age <65) or HCFA (if age >65)	Self-reported occupational information *via* mailed questionnaires and telephone interviews

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Charbotel *et al.* (2006) [Charbotel *et al.*, 2009][a]	France	Inc	RCC	1993-2003	B	Cases: 61.8 Controls: 61.1	86	Local urologists and hospitals	316	Urologists or general practitioner	Self/proxy-reported occupational history and task-exposure matrix linked with U-TCA or air-monitoring data
Moore *et al.* (2010)[b]	Russia, Romania, Poland, Prague, Czech Republic	Inc	RCC	1999-2003	B	Cases: $\bar{x}$ = 60 Controls: $\bar{x}$ = 59	1,097	Hospital	1,476	Hospital	Self-reported occupational information
Christensen *et al.* (2013)	Canada	Inc	Kidney	1979-1985	M	35-70	177	Hospitals	442 population-based, 1,594 cancer-based	Population-based electoral lists	Expert assessment of self-reported job history
Vlaanderen *et al.* (2013)	Finland, Iceland, Norway, Sweden	Inc	Kidney	1960-2005	B	30-64	76,130	All subjects who participated in the 1960, 1970, 1980–1981 and/or 1990 censuses	380,650	All subjects who participated in the 1960, 1970, 1980-1981 and/or 1990 censuses	JEM
Purdue *et al.* (2017)	US	Inc	Kidney	2002-2006 (white cases) 2002-2007 (black cases)	B	Cases: 20-64 Controls: 65-79	1,217	Metropolitan Detroit Cancer Surveillance System	1,235	DMV records and Medicare eligibility files	Self-reported occupational information

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Michalek *et al.* (2019)	Finland, Iceland, Sweden	Inc	RCC or CaRP	1961-2005[a]	B	20+	59,778	National cancer registries	298,890	NOCCA cohort	NOCCA-JEM
Purdue *et al.* (2021)[b]	Czech Republic, Poland, Romania, and Russia	Inc	RCC	1999-2003	B	Cases: $\bar{x}$ = 60.2	1,097	Hospitals	1,476	Hospitals	Self-reported occupational information
Andrew *et al.* (2022)	US	Inc	Kidney	2010-2019	B	≥1	292	Dartmouth-Hitchcock Health System	448	Dartmouth-Hitchcock Health System	Residential exposure to TCE from water

Notes:
B = Both Male and Female; CaRP = Cancer of the Renal Pelvis; DMV = Department of Motor Vehicles; HCFA = Health Care Finance Administration; Inc = Incidence; JEM = Job Exposure Matrix; M = Male; Mort = Mortality; NOCCA = Nordic Occupational Cancer Study; RCC = Renal Cell Carcinoma; RDD = Random Digit Dialing; SEER = Surveillance, Epidemiology, and End Results; SSA = Social Security Administration; TCE = Trichloroethylene; 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) The abstract for Charbotel *et al.* (2009) is in English, but the paper is in French, so only limited information was available for the study. Charbotel *et al.* (2006) more extensive analyses and included exposure-response analyses using different exposure metrics therefore those results are preferable and are reviewed here.
(b) Moore *et al.* (2010) and Purdue *et al.* (2021) use the same study population. Moore *et al.* (2010) evaluated RCC as a whole and Purdue *et al.* (2021) evaluated RCC risk by clear cell subtype.

Table D.4 TCE and Kidney 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
Asal *et al.* (1988)	Inc	OR	**Industry (Males)[a]**				–	Age, smoking status, and weight
			Machining	13	7	1.7 (0.7-4.3)		
			Painting/paint manufacturing	22	16	1.3 (0.7-2.6)		Age
			Metal degreasing/cleaning	19	10	1.7 (0.7-3.8)		Age, smoking status, and weight
			Dry Cleaning Industry				–	
			Males	3	6	0.7 (0.2-2.3)		
			Females	8	1	2.8 (0.8-9.8)		
Brownson (1988)	Inc	OR	Machinists (males)	3	4	2.2 (0.5-10.3)	–	Age, smoking status, and alcohol use
Jensen *et al.* (1988)	Inc	RR	Employment as an iron or metal blacksmith (males)	17	41	1.4 (0.7-2.9)	–	Sex and lifetime tobacco consumption
			Employment as a painter or paint manufacturer (males and females)	10	19	1.8 (0.7-4.6)		
Partanen *et al.* (1991)	Inc	OR	**Industry/Occupation (Men)**				–	Obesity, smoking status, and coffee consumption
			Metal products, machinery and equipment	23	–	1.81 (0.95-3.48)		
			Paper and pulp; printing and publishing	18	–	**2.20 (1.02-4.72)**		
			Paper and paper products	13	–	1.69 (0.73-3.91)		
			Printing and publishing	6	–	4.63 (0.91-23.5)		
			Printers	4	–	5.96 (0.65-54.5)		
			Iron and metal ware work	22	–	1.87 (0.94-3.76)		
			Machinists; machine and engine repairmen	10	–	2.33 (0.83-6.51)		
			Industry/Occupation (Women)					
			Paper and pulp; printing and publishing	7	–	**5.95 (1.21-29.8)**	–	
			Printing and publishing	5	–	8.01 (0.92-69.8)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
McCredie and Stewart (1993)	Inc	RR	**Occupation/Industry**					Age, sex, and method of interview
			Renal cell cancer					
			Iron and steel industry	52	39	1.18 (0.75-1.85)	–	
			Printing or graphics industry	29	24	1.18 (0.67-2.08)		
			Machinist or tool maker	48	34	1.15 (0.72-1.86)		
			Renal pelvic cancer					Age, sex, education, method of interview, smoking, and phenacetin containing analgesics
			Iron and steel industry	19	39	**2.13 (1.04-4.39)**	–	
			Printing or graphics industry	6	24	0.82 (0.32-2.11)		Age, sex, education, and method of interview
			Machinist or tool maker	16	34	1.83 (0.92-3.61)		
Aupérin *et al.* (1994)	Inc	OR	Male machinery fitters, machine assemblers, and precision instrument makers	8	16	0.7 (0.3-1.9)	–	Sex, age at interview, hospital, interviewer, number of yrs at school, smoking status, and BMI before diagnosis
			Electrical fitters and related electrical and electronics workers	4	10	0.8 (0.2-2.5)	–	
Greenland *et al.* (1994)[b]	Mort	OR	No exposure	–	–	Ref	–	Age and yr of death
			Any exposure	–	–	0.99 (0.30-3.32)		
Mellemgaard *et al.* (1994)	Inc	OR	**Industry of Employment (Males) 10-Yr Lag**					Age, gender, BMI, and smoking
			Iron and steel industry	31	26	1.4 (0.8-2.4)	–	
			Dry cleaning	2	1	2.3 (0.2-27)		
			Printing	8	8	1.1 (0.4-3.1)		
			Industry of Employment (Females) 10-Yr Lag					
			Iron and steel industry	2	2	1.0 (0.1-8.2)	–	
			Dry cleaning	2	1	2.9 (0.3-33)		
			Printing	3	4	1.1 (0.2-5.2)		
Delahunt *et al.* (1995)	Inc	RR	Toolmakers and blacksmiths	–	–	1.48 (0.72-3.03)	–	Age and smoking status
			Printers	–	–	0.67 (0.25-1.83)		
			Dry cleaning occupation	–	–	1.92 (0.27-13.89)		
Mandel *et al.* (1995)	Inc	OR	**Industry or Occupation (≥1 Yr)**				–	Age, center, education level, smoking, BMI
			Unexposed (< 1 yr in industry or occupation)	–	–	Ref		
			Iron or steel industry	113	87	**1.6 (1.2-2.2)**		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Printing or graphics	39	41	1.3 (0.8-2.0)		
			Welder	77	85	1.1 (0.8-1.6)		
			Duration of Iron or Steel Industry Exposure (Yrs)					
			1-3	37	26	**2.1 (1.2-3.6)**		
			4-21	38	32	1.4 (0.8-2.2)		
			22-59	37	28	1.5 (0.9-2.6)		
Schlehofer *et al.* (1995)	Inc	RR	**Industry with 5 Yr Lag**					Age, gender, and smoking
			Metal	71	51	**1.63 (1.07-2.48)**	–	
			Electric	14	26	0.51 (0.26-1.01)		
			Occupation with 5 Yr Lag					
			Metal	71	56	1.38 (0.89-2.12)	–	
			Electric	9	16	0.57 (0.25-1.33)		
			Occupational metal exposure (men only)	62	49	1.47 (0.94-2.3)	–	Age and smoking
			Duration of Exposure for Occupational Metal Exposure (Yrs)					
			<5	–	–	Ref	–	
			5-15	–	–	1.29 (0.6-2.8)		
			>15	–	–	1.54 (0.9-2.5)		
Vamvakas *et al.* (1998)	Inc	OR	**Exposure Level**				–	Age, diastolic blood pressure
			High	8	2	**11.42 (1.96-66.79)**		
			Medium	9	3	**11.92 (2.55-55.6)**		
			Low	2	2	6.61 (0.50-87.76)		
Dosemeci *et al.* (1999)	Inc	OR	Overall	55	–	1.30 (0.9-1.9)	–	Restricted to white participants and adjusted for age, smoking status, hypertension status, use of diuretics, and/or use of anti-hypertension drugs, and BMI
			Males	33	–	1.04 (0.6-1.7)		
			Females	22	–	1.96 (1.0-4.0)		
Parent *et al.* (2000)	Inc	OR	**Occupation**					Respondent status (self *vs.* proxy), age, smoking, BMI
			Metal Processors	4	–	1.2 (0.4-3.4)	–	
			Printers	6		**3.0 (1.2-7.5)**		
			Aircraft mechanics	4		2.8 (1.0-8.4)		
			Industry					

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Printing and publishing	4	–	1.1 (0.4-3.0)	–	
			Printing related services	4		**7.3 (2.2-24.6)**		
			Metal fabricating and machining	14		1.0 (0.6-1.8)		
			Metal fabricating and machining (>10 yrs)	8		1.2 (0.6-2.4)		
			Laundry and cleaning	4		1.7 (0.6-4.7)		
Pesch *et al.* (2000a)	Inc	OR	**German JEM TCE Exposure Index**					Age, study center, smoking status, region, sex
			Males					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	135	–	1.1 (0.9-1.4)		
			High	138	–	1.1 (0.9-1.4)		
			Substantial	55	–	1.3 (0.9-1.8)		
			Females					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	28	–	1.2 (0.8-1.8)		
			High	29	–	1.3 (0.8-2.0)		
			Substantial	6	–	0.8 (0.3-1.9)		
			JTEM TCE Exposure Index					
			Males					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	68	–	1.3 (1.0-1.8)		
			High	59	–	1.1 (0.8-1.5)		
			Substantial	22	–	1.3 (0.8-2.1)		
			Females					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	11	–	1.3 (0.7-2.6)		
			High	7	–	0.8 (0.4-1.9)		
			Substantial	5	–	1.8 (0.6-5.0)		
Mattioli *et al.* (2002)	Inc	OR	**Occupation/Industry**					Age, sex, birthplace, residence, BMI, smoking, coffee & alcohol consumption,
			Other occupation/industry	–	–	Ref	–	
			Metal workers	37	26	2.21 (0.99-5.37)		
			Printers	7	5	1.55 (0.17-13.46)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Painters	5	9	0.31 (0.06-1.56)		and use of phenacetin and/or diuretics
Brüning *et al.* (2003)	Inc	OR	**Self-Reported Exposures to TCE**					Age, sex, and smoking
			Ever exposed	25	38	**2.47 (1.36-4.49)**	–	
			Duration of exposure (yrs)[d]					
			No exposure	109	363	Ref		
			<10	11	14	**3.78 (1.54-9.28)**		
			10 to <20	7	13	1.80 (0.67-4.79)		
			20+	6	7	2.69 (0.84-8.66)		
			Time since first exposure (yrs)[e]					
			No exposure	109	363	Ref		
			5 to <10	1	2	3.21 (0.28-37.38)		
			10 to <20	2	6	1.50 (0.28-8.10)		
			20+	22	27	**2.86 (1.49-5.49)**		
			Time since last exposure (yrs)[f]					
			No exposure	109	363	Ref		
			<5	1	2	3.26 (0.27-38.98)		
			5 to <10	4	9	1.87 (0.52-6.71)		
			10 to <20	7	4	**7.25 (1.96-26.78)**		
			20+	13	20	2.17 (1.00-4.70)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Occupational Histories Linked to JEM[e]					
			Degreasing agents					
			Ever work in metal greasing/degreasing	15	11	**5.57 (2.33-13.32)**	–	
			Low exposure	9	14	2.11 (0.86-5.18)		
			High exposure	7	20	1.01 (0.40-2.54)		
			Organic solvents					
			Low exposure	8	13	1.80 (0.70-4.59)	–	
			High exposure	8	17	1.45 (0.59-3.58)		
Zhang *et al.* (2004)	Inc	OR	**Male Assembler**					Age, body mass index, smoking, type of respondent, red meat intake, fruit intake, history of hypertension, and first-degree relative with kidney cancer
			All	5	17	2.5 (0.8-7.6)	–	
			≤10 yrs of employment	1	8	0.8 (0.1-8.0)		
			≥10 yrs of employment	4	9	**4.2 (1.2-15.3)**		
Charbotel *et al.* (2006)	Inc	OR	Overall	37	110	1.64 (0.95-2.84)	–	Matched on age, sex, and adjusted for smoking status and BMI
			Tertiles of Cumulative TCE Exposure (ppm-Yrs)[g]					
			Low (1-150)	12	37	1.62 (0.75-3.47)	**0.04**	
			Medium (155-335)	9	36	1.15 (0.47-2.77)		
			High (>335)	16	37	**2.16 (1.02-4.06)**		
			Cumulative Exposure Plus Peak Exposure to TCE					
			Low/medium + no peaks	18	65	1.35 (0.69-2.63)	–	Age, sex, smoking status, and BMI
			Low/medium + peaks	3	8	1.61 (0.36-7.30)		
			High + no peaks	8	23	1.76 (0.65-4.73)		
			High + peaks	8	14	**2.73 (1.06-7.07)**		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
Moore *et al.* (2010)[h]	Inc	OR	Any Exposure	48	40	**1.63 (1.04-2.54)**	**0.03**	Age, sex, study center
			Any Exposure (High confidence exposure)	29	19	**2.05 (1.13-3.73)**	**0.02**	
			Yrs					
			<13.5	22	20	1.44 (0.77-2.69)	**0.03**	
			≥13.5	26	20	1.82 (0.99-3.34)		
			Hours					
			<1,080	17	20	1.07 (0.55-2.09)	**0.01**	
			≥1,080	31	20	**2.22 (1.24-3.99)**		
			Cumulative (ppm-Yrs)					
			<1.58	17	19	1.19 (0.61-2.35)	**0.02**	
			≥1.58	31	21	**2.02 (1.14-3.59)**		
			Average Intensity (ppm)					
			<0.076	31	30	1.38 (0.81-2.35)	**0.02**	
			≥0.76	17	10	**2.34 (1.05-5.21)**		
Christensen *et al.* (2013)	Inc	OR	Never exposed – chlorinated solvents	134	403 population, 1497 cancer	Ref[i]	–	Smoking status; age; income; education; ethnicity; self-reported *vs.* proxy data; coffee, beer, wine, & spirits intake
			Any TCE exposure	5	15 population, 63 cancer	0.9 (0.4-2.4)		
			Substantial TCE exposure[j]	2	9 population, 34 cancer	0.6 (0.1-2.8)		
Vlaanderen *et al.* (2013)	Inc	HR	**Tertiles of Cumulative TCE Exposure**					Age, country, and sex
			First	1,217	–	1.01 (0.95-1.07)	–	
			Second	1,556	–	1.02 (0.97-1.08)		
			Third	1,372	–	1.00 (0.95-1.07)		
Purdue *et al.* (2017)	Inc	OR	**Exposure Probability**					Age, sex, race, study center, education, smoking status, BMI, history of hypertension
			Unexposed	521	582	Ref	–	
			<50%	608	565	1.2 (0.9-1.4)		
			50%-89%	18	27	0.8 (0.4-1.6)		
			≥90%	32	32	0.8 (0.4-1.5)		
			Yrs Exposed					

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Unexposed	521	582	Ref	0.41	Age, sex, race, study center, education, smoking, BMI, hypertension
			Tertile 1 (≤5)	18	20	0.9 (0.4-1.9)		
			Tertile 2 (6-10)	9	19	0.4 (0.1-1.1)		
			Tertile 3 (>10)	23	20	0.9 (0.5-1.9)		
			Average Weekly Exposure (Hours/Week)					
			Unexposed	521	582	Ref	0.89	
			≤1	18	32	0.6 (0.3-1.3)		
			>1-6	20	20	0.7 (0.3-1.5)		
			>6	12	7	1.4 (0.5-3.7)		
			Cumulative Hours Exposed					
			Unexposed	521	582	Ref	0.69	
			Tertile 1 (≤416)	12	20	0.7 (0.3-2.0)		
			Tertile 2 (417-2,184)	15	20	0.6 (0.3-1.3)		
			Tertile 3 (>2,184)	23	19	0.9 (0.5-1.9)		
Michalek *et al.* (2019)	Inc	OR	**TCE Exposure (ppm-Yrs)**					Age, sex, country, other occupational exposure agents of interest[k]
			Unexposed	56,316	282,593	Ref	0.61	
			Low (<3192.54 ppm-yr)	1760	8118	1.00 (0.94-1.07)		
			Moderate (3192.54-12,785.08 ppm-yr)	1347	6560	0.92 (0.85-1.00)		
			High (>12,785.08 ppm-yr)	355	1619	1.03 (0.88-1.19)		
Purdue *et al.* (2021)	Inc	OR	**TCE Exposure Level – RCC Cases with ccA Subtype**					Country, age, sex, and education level
			Unexposed	109	1,146	Ref	0.94	
			<1.58 ppm-yrs	2	21	0.69 (0.16-3.04)		
			≥1.58 ppm-yrs	3	19	1.25 (0.36-4.39)		
			TCE Exposure Level – RCC Cases with ccB Subtype					
			Unexposed	81	1,146	Ref	**0.049**	
			<1.58 ppm-yrs	3	21	1.67 (0.48-5.82)		
			≥1.58 ppm-yrs	5	19	**3.09 (1.11-8.65)**		
Andrew *et al.* (2022)	Inc	OR	**15-Yr Median (Decayed TCE Exposure)[l]**				0.081	Age, sex, alcohol consumption, smoking status, BMI, and diabetes
			<50th Percentile (0 µg/L)	189	298	Ref		
			50-75th Percentile (>0-27.6 µg/L)	35	33	**1.78 (1.05-3.03)**		
			≥75th Percentile (≥27.6 µg/L)	62	110	0.92 (0.63-1.34)		

Notes (continued on next page):

BMI = Body Mass Index; ccA = Clear Cell Renal Carcinoma Subtype A; ccB = Clear Cell Renal Carcinoma Subtype B; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; Inf. = Infinite; JEM = Job Exposure Matrix; JTEM = Job Task Exposure Matrix; OR = Odds Ratio; ppm = Parts Per Million; RCC = Renal Cell Carcinoma; Ref = Reference; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; yr(s) = Year(s).
Bolded values indicate statistical significance.
– = Not Reported.
(a) Results reported for population-based control comparison. Asal *et al*. (1988) reported that the hospital-based controls results were similar.
(b) Restricted to white males (Greenland *et al*., 1994).
(c) Pesch *et al*. (2000a) 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."
(d) Missing information on exposure for one case and four controls (Brüning *et al*., 2003).
(e) Missing information on exposure for three controls (Brüning *et al*., 2003).
(f) Brüning *et al*. (2003) used the median of the exposure index as the cutoff between low and high categories.
(g) The categorical mean cumulative exposures (and ranges) in Charbotel *et al*. (2006) were estimated to be 62.4 (1-150), 253.2 (155-355), and 925.0 (>355 – upper limit not reported) ppm-years, respectively (as reported in US EPA, 2011).
(h) Moore *et al*. (2010) and Purdue *et al*. (2021) use the same study population. Moore *et al*. (2010) evaluated RCC as a whole and Purdue *et al*. (2021) evaluated RCC risk by clear cell subtype.
(i) Reported results are for weighted cancer and population-based controls combined. Results using only population-based controls were similar (Christensen *et al*., 2013).
(j) Substantial exposure defined as "exposed at a confidence level of probable or definite, a concentration and frequency of medium or high, and a duration greater than 5 yrs" (Christensen *et al*., 2013).
(k) Other occupational exposure agents of interest included aliphatic and alicyclic hydrocarbon solvents, asbestos, chlorinated hydrocarbon solvents, chromium, diesel engine exhaust, nickel, lead, perceived physical workload, quartz dust, ultraviolet radiation, welding fumes, wood dust (Michalek *et al*., 2019).
(l) Andrew *et al*. (2022) noted that they "also calculated the kidney cancer risk assuming a 15-year latency period between exposure and disease onset and obtained similar results (50–75th percentile OR 1.9 95% CI 1.12–3.23; 75th OR 0.94 95 %CI 0.65–1.37 for the epoch 15 to 20-years prior to diagnosis) (Data Not Shown)."

Table D.5 TCE and Kidney Cancer Meta-Analyses and Pooled Study Results

Study	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	Kidney	4	Cohort	Inverse-variance weighting	Tier I[a]	SIR	**1.7 (1.1-2.7)**
		Mort		5				SMR	1.2 (0.8-1.7)
		Inc		1			Tier II[b]	SIR	**3.7 (1.7-8.1)**
		Mort		5				SMR	1.3 (0.9-1.7)
		Inc		2			Tier III[c]	SIR	0.9 (0.7-1.2)
		Mort		4			Tier IV[d]	SMR	**2.3 (1.5-3.5)**
Kelsh *et al.* (2010)	Meta-analysis	Inc & Mort	Kidney	23	Cohort & case-control	Random effects	All studies	SRRE	**1.30 (1.04-1.61)**
				7			Shortest exposure/employment duration study category[e]		1.50 (0.96-2.36)
				7			Longest exposure/employment duration study category[e]		1.24 (0.69-2.23)
				3			Lowest cumulative exposure study category[f]		1.29 (0.68-2.47)
				3			Highest cumulative exposure study category[f]		1.39 (0.75-2.59)
				8	Cohort		Group 1 studies[g]		**1.34 (1.07-1.67)**
				7			Group 2 studies[h]		1.58 (0.75-3.32)
				7	Case-control		All studies		**1.57 (1.06-2.30)**
		Inc		16	Cohort		All cohort studies		1.34 (1.00-1.81)
Scott and Jinot (2011)[i]	Meta-analysis	Inc & Mort	Kidney	15	Cohort & case-control	Random effects	All studies	RRm	**1.27 (1.13-1.43)**
				13			Highest exposure group[j]		**1.58 (1.28-1.96)**
Karami *et al.* (2012a)	Meta-analysis	Inc & Mort	Kidney & RCC	9	Cohort	Random effects	**TCE Exposure-Specific Studies**		
							All studies	RR	**1.26 (1.02-1.56)**
				5			SMR studies		1.16 (0.78-1.74)
				4			SIR studies		**1.31 (1.01-1.69)**

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
				9	Case-control		All studies	OR	**1.35 (1.17-1.57)**
			Kidney	8	Cohort			RR	1.12 (0.82-1.53)
				2	Case-control			OR	0.86 (0.44-1.67)
			RCC	1	Cohort			RR	**1.40 (1.00-1.80)**
				7	Case-control			OR	**1.39 (1.19-1.63)**
Hansen *et al.* (2013)	Pooled	Inc	Kidney	3	Cohort	Poisson	Overall	SIR	1.01 (0.70-1.42)
							Overall (10-yr lag)		1.04 (0.71-1.50)
							Men		1.03 (0.66-1.53)
							Women		0.96 (0.41-1.88)
						Cox proportional hazards	**U-TCA-Level (mg/L)**		
							<5	HRR	Ref
							5-25		1.12 (0.46-2.70)
							25-50		0.81 (0.21-2.97)
							>50		2.04 (0.81-5.17)

Notes:
CI = Confidence Interval; HRR = Hazard Rate Ratio; Inc = Incidence; JEM = Job-Exposure Matrix; mg/L = Milligrams per Liter; Mort = Mortality; OR = Odds Ratio; RCC= Renal Cell Carcinoma; Ref = Reference; RR = Relative Risk; RRm = Meta-Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SRRE = Summary Relative Risk Estimate; TCE = Trichloroethylene; U-TCA = Urinary Trichloroacetic Acid; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
(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) Shortest duration of exposure/employment study categories ranged from <1 to 10 yrs; longest duration of exposure/employment study categories ranged from 4+ to 20+ yrs (Kelsh *et al.*, 2010).
(f) For two studies (Charbotel *et al.*, 2006; Morgan *et al.*, 1998) the cumulative exposure categories were defined as "low" and "high" and for Blair (1998) the cumulative exposure categories were defined as <5 unit-yrs and >24 unit-yrs (Kelsh *et al.*, 2010).
(g) Group 1 cohort studies, "specifically identified trichloroethylene as a workplace exposure through biomonitoring, industrial hygiene data, identified work practices, or job titles that involved trichloroethylene", and "demonstrated sufficiently complete enumeration of the workforce" (Kelsh *et al.*, 2010).
(h) Group 2 cohort studies, "lacked specific, detailed trichloroethylene exposure information" (Kelsh *et al.*, 2010).
(i) The results of the meta-analysis presented in Scott and Jinot (2011) are reported and discussed in US EPA (2011).
(j) Scott and Jinot (2011) preferred to include risk estimates based on the highest category of cumulative exposure; however, the highest category of duration of exposure was often the sole exposure metric available.

Attachment E

TCE Animal Carcinogenicity Studies

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

Citation	Strain/Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-day)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
NCI (1976)[a]	Osborne-Mendel rats	78	110 weeks	20 M	0	1/20	2/20
				50 M	549	1/50	1/50
					1,097	0/50	0/50
				20 F	0	0/20	0/20
				50 F	549	0/48	0/48
					1,097	0/50	0/50
	B6C3F1 mice		90 weeks	20 M	0	0/20	0/20
				50 M	1,169	0/50	0/50
					2,339	1/48	0/48
				20 F	0	0/20	0/20
				50 F	869	0/50	0/50
					1,739	0/47	0/47
Van Duuren *et al.* (1979)[b]	Ha:ICR Swiss mice	88 (once weekly)	Until spontaneous death	30 M	0	NR	NR
					2.4	NR	NR
				30 F	0	NR	NR
					2.4	NR	NR
Henschler *et al.* (1984)[c]	Swiss (ICR/HA) mice	72	106 weeks	50 M	0	1/50	1/50
					2,400 (TCE industrial)	0/49	0/49
					2,400 (TCE pure)	1/50	1/50
					2,400 (TCE + EB)	2/49	2/49
					2,400 (TCE + EPC)	0/49	0/49
					2,400 (TCE + EB + EPC)	0/49	0/49
				50 F	0	0/50	1/50
					1,800 (TCE industrial)	0/50	0/50
					1,800 (TCE pure)	4/50	0/50
					1,800 (TCE + EB)	0/48	0/48
					1,800 (TCE + EPC)	0/50	0/50
					1,800 (TCE + EB + EPC)	0/50	0/50

Citation	Strain/Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-day)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni *et al.* (1986, 1988a)	Sprague-Dawley rats	52	Until natural death	30 M	0	NR	NR
					50	NR	NR
					250	NR	NR
				30 F	0	NR	NR
					50	NR	NR
					250	NR	NR
NTP (1988)[d]	ACI rats	103	103 weeks	50 M	0	0/50	0/50
					500	0/49	2/49
					1,000	0/49	1/49
				50 F	0	0/48	5/48
					500	4/47	4/47
					1,000	0/43	2/43
	August rats			50 M	0	0/50	0/50
					500	1/50	2/50
					1,000	1/49	0/49
				50 F	0	1/49	0/49
					500	2/48	2/48
					1,000	0/50	0/50
	Marshall rats			50 M	0	0/49	0/49
					500	1/50	0/50
					1,000	0/47	2/47
				50 F	0	1/50	1/50
					500	3/48	1/48
					1,000	1/44	3/44
	Osborne-Mendel rats			50 M	0	1/50	0/50
					500	6/50**	0/50
					1,000	1/50	2/50
				50 F	0	0/50	0/50
					500	0/50	1/50
					1,000	1/49	0/49
NTP (1990)[e]	F344/N rats	103	103 weeks	50 M	0	0/48	0/48
					500	2/49	1/49
					1,000	0/49	3/49*, †

Citation	Strain/Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-day)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
				50 F	0	0/50	0/50
					500	0/49	0/49
					1,000	0/48	1/48
	B6C3F1 mice			50 M	0	1/49	0/49
					1,000	0/50	1/50
				50 F	0	0/48	0/48
					1,000	0/49	0/49

Notes:

bw = Body Weight; EB = 1,2-epoxybutane; EPC = Epichlorohydrin; F = Female; M = Male; NCI = National Cancer Institute; NR = Kidney was analyzed, but kidney tumor findings were not reported; NTP = National Toxicology Program; TCE = Trichloroethylene; TEN = Triethanolamine; US EPA = United States Environmental Protection Agency.

$^{*}p < 0.05$; $^{**}p < 0.01$; † p-trend <0.05

(a) I used the number of animals examined, as specified in Table XXIXa (rats) and XXXa (mice), as denominators. NCI (1976) concluded that the results in rats were inconclusive due to significant early mortality (NCI, 1976). The technical-grade TCE used in this study contained two stabilizer compounds that are known carcinogens (epichlorohydrin and 1,2-epoxybutane).

(b) Average daily dose for a 30 g mouse in Van Duuren *et al.* (1979) based on a reported once-weekly dose of 0.5 g, as estimated by US EPA (2011). US EPA (2011) concluded that the "[i]nadequate design and reporting of this study limit the ability to use the results as an indicator of TCE carcinogenicity."

(c) 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. None of the kidney tumor incidences were statistically significant; this table only shows exposure conditions for which kidney tumors were observed. 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.

(d) I used the number of animals necropsied when the denominators for incidences were not specified. NTP (1988) did not draw any conclusions from this study regarding TCE carcinogenicity due to chemically induced toxicity because "the doses of trichloroethylene selected for the 2-year studies were too high," reduced survival of animals in each treatment group, including "a large number of accidental deaths" in the high dose group due to accidental gavage error, and 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."

(e) 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." Regarding the results of the NTP (1990) study, US EPA (2011) acknowledged the high rates of death by gavage error but stated, "[H]istorical control incidences at NTP of kidney tumors in F344 rats is very low, lending biological significance to their occurrence in this study, despite the study's limitations."

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

Citation	Strain/Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
Henschler *et al.* (1980)	Han:WIST rats	78	156 weeks	30 M	0	2/29	1/29
					100	1/30	0/30
					500	2/30	1/30
				30 F	0	0/28	0/28
					100	0/30	0/30
					500	1/30	0/30
	Han:NMRI mice		130 weeks	30 M	0	4/30	1/30
					100	2/29	0/29
					500	1/30	0/30
				30 F	0	0/29	0/29
					100	0/30	0/30
					500	0/28	0/28
	Syrian hamsters			30 M	0	1/30	0/30
					100	0/30	0/30
					500	1/30	0/30
				30 F	0	0/30	0/30
					100	0/29	0/29
					500	0/30	0/30
Fukuda *et al.* (1983)[a]	Crj:CD (Sprague-Dawley) rats	104	107 weeks	49-51 F	0	0/50	0/50
					50	0/50	0/50
					150	0/47	0/47
					450	0/51	1/51
	Crj:CD (ICR) mice			49-50 F	0	0/49	0/49
					50	0/50	0/50
					150	0/50	0/50
					450	0/46	0/46
Maltoni *et al.* (1986, 1988a)[b, c]	Sprague-Dawley rats	104	Until natural death	40 M	0	0/40	0/40
					100	0/40	0/40
					300	0/40	0/40
					600	0/40	1/40
				40 F	0	0/40	0/40
					100	0/40	0/40

Citation	Strain/Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
					300	0/40	0/40
					600	0/40	0/40
	Sprague-Dawley rats			90-95 M	0	0/95	0/95
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	3/90
				90-105 F	0	0/105	0/105
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	1/90
	B6C3F1 mice	78		90 M	0	0/90	0/90
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	0/90
				90 F	0	0/90	0/90
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	0/90
	Swiss mice			90 M	0	0/90	0/90
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	0/90
				90 F	0	0/90	0/90
					100	0/90	0/90
					300	0/90	0/90
					600	0/90	0/90

Notes:

F = Female; M = Male; ppm = Parts Per Million; TCE = Trichloroethylene; US EPA = United States Environmental Protection Agency.

(a) Fukuda *et al.* (1983) reported clear cell carcinoma in 1/51 female rats at 450 ppm ($p > 0.05$). The TCE utilized in this study contained a stabilizer compound that is a known carcinogen (epichlorohydrin). In addition, Fukuda *et al.* (1983) noted "a few [animals] that were killed accidentally, severely autolyzed or cannibalized, and died before the first appearance of tumors among the groups." Finally, as noted by IARC (2014a), there was incomplete reporting of tumor incidences, *i.e.*, "Only malignant tumours were counted when both malignant and benign tumours were observed in the same organ."

(b) Although not statistically significant, Maltoni *et al.* (1986, 1988a) concluded that the kidney tumors in rats were caused by TCE exposure due to their rarity in historical controls. Animals were observed "until spontaneous death" (Maltoni *et al.*, 1986, 1988a).

(c) I calculated these incidences from percentages provided in Maltoni *et al.* (1986).

Table E.3 TCE and Kidney 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, with the exception of the chronic studies conducted by Fukuda *et al.* (1983) and NTP (1988). Fukuda *et al.* (1983) reported tumor incidences incompletely (only malignant tumors were reported when both malignant and benign tumors were observed in the same organ), although there was no evidence of any kidney tumors except for clear cell carcinoma in 1/50 female rats at the highest tested dose (p >0.05). 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."
Allocation	Animals were randomly allocated to dose groups in the majority of chronic studies with the exception of Henschler *et al.* (1980), Fukuda *et al.* (1983), and Van Duuren *et al.* (1979).
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. Furthermore, the tested doses were too high resulting in early mortality in both of these studies (NTP, 1988, 1990). Fukuda *et al.* (1983) and Henschler *et al.* (1984) exposed mice to TCE that contained stabilizer compounds known to be carcinogenic (epichlorohydrin and 1,2-epoxybutane, respectively). Fukuda *et al.* (1983) also indicated "a few [animals] that were killed accidentally, severely autolyzed or cannibalized, and died before the first appearance of tumors among the groups," suggesting inadequate animal husbandry. NCI (1976) also 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. No other studies had indications that there were differences across treatment groups that could bias results.
Sample	Chronic studies had adequate sample sizes, with the exception of NCI (1976) (for controls), Van Duuren *et al.* (1979), Henschler *et al.* (1980), and Maltoni *et al.* (1986) (for oral exposure and experiment BT304 bis).
Chemical Administration and Characterization	Studies provided adequate information on chemical source, purity, or 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	For four chronic studies, the exposure duration was too short (NCI, 1976; Henschler *et al.*, 1980; Maltoni *et al.*, 1986; NTP, 1988; NTP, 1990) to assess carcinogenicity in rats: 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). The exposure period for mice in Van Duuren *et al.* (1979), Fukuda *et al.* (1983), and NTP (1990) was too long (88-104 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.

Parameter	Summary
Outcome Assessment	In some studies, there was a reliable, valid, sensitive, and specific outcome evaluation method and an appropriate observation period. However, seven studies (Maltoni *et al.*, 1986a, 1988a; NCI, 1976; Fukuda *et al.*, 1983; Henschler *et al.*, 1984; NTP, 1990; Van Duuren *et al.*, 1979; Henschler *et al.*, 1980) had observation periods that were too long. Maltoni *et al.* (1986a, 1988a) and Van Duuren *et al.* (1979) examined animals after "spontaneous death." Fukuda *et al.* (1983) examined rats and mice after 107 weeks (3 weeks post-exposure), and NCI (1976) observed rats and mice until 110 weeks (32 weeks post-exposure) and 90 weeks (12 weeks post-exposure). Henschler *et al.* (1984) observed mice for 106 weeks (34 weeks post-exposure). NTP (1990) observed mice for 103 weeks. Henschler *et al.* (1980) observed mice and hamsters for 130 weeks (52 weeks post-exposure) and rats for 156 weeks (78 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) applied improper statistical analyses that did not account for the extended observation period (Gift *et al.*, 2013). Lastly, NTP (1990) only observed rats for 103 weeks, which is too short for evaluating carcinogenicity.

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

Table E.4 TCE and Kidney Cancer Chronic Toxicity 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
Van Duuren *et al.* (1979)	**Reporting** **Bias** **Chemical Administration and Characterization**	**Sample:** Small sample size **Allocation:** Did not specify whether random **Exposure Conditions:** Only one dose tested; exposure duration too long **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Henschler *et al.* (1984)	**Reporting** **Allocation** **Sample** **Chemical Administration and Characterization**	**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	**Limited:** Low study quality
Maltoni *et al.* (1986, 1988a)	**Allocation** **Bias** **Chemical Administration and Characterization**	**Reporting:** No kidney tumor data **Sample:** Small sample size **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long; improper statistics	**None:** No kidney 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 short (rats); too long (mice) **Outcome Assessment:** Observation period too short (rats); too long (mice)	**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
Fukuda *et al.* (1983)	**Sample** **Chemical Administration and Characterization** **Exposure Conditions** (rats)	**Reporting:** Incomplete reporting of tumor incidences **Bias:** TCE contained stabilizer compounds that are carcinogenic; animal husbandry inadequate **Allocation:** Did not specify whether random **Exposure Conditions:** Exposure duration too long (mice) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Maltoni *et al.* (1986, 1988a)	**Reporting** **Allocation** **Bias** **Sample** **Chemical Administration and Characterization** **Exposure Conditions**	**Outcome Assessment:** Observation period too long; improper statistics	**Limited:** Low study quality

Notes:
MTDs = Maximum Tolerated Doses; NCI = National Cancer Institute; NTP = National Toxicology Program; TCE = Trichloroethylene.

Attachment F

PCE Epidemiology Studies

List of Tables

Table F.1 PCE and Kidney Cancer Cohort Study Characteristics

Table F.2 PCE and Kidney Cancer Cohort Study Results

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

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

Table F.1 PCE and Kidney 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	Kidney	Death certificate	1942-1980
Anttila *et al.* (1995)	Finland	FIOH workers	B	–	849	1974-1983	Blood PCE concentration	Mort	Kidney	Finnish cancer registry and Central Statistical Office of Finland	1974-1992
Travier *et al.* (2002)	Sweden	Dry-cleaning workers	B	–	3,742	1960/1970 census	Census JEM	Inc	Kidney	CERIII	1971-1989
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	Mean at end of follow-up: 39.25	Total: 86,868	1973-1997	Employment in the factory	Mort	Kidney and other and unspecified urinary organs	National mortality database	1985-1997
Ji *et al.* (2005)	Sweden	Working Swedish population	B	–	M: 1,644,958 F: 1,154,091	1960/1970 census	Occupation listed on census	Inc	Renal parenchyma[a]	Swedish Family-Cancer Database	1961-2000
Sung *et al.* (2007)	Taiwan	Electronics factory workers	F	–	63,982	1974-1992	Employment at factory	Inc	Kidney and other urinary organs	Taiwan National Cancer Registry	1979-2001
Wilson *et al.* (2008)	Sweden	Employed Swedish Residents	B	–	4,197,684	1960/1970 census	JEM	Inc	Renal pelvis	CERIII	1971-1989
Pukkala *et al.* (2009) [Andersen *et al.*, 1999; Lynge and Thygesen, 1990]	Denmark, Finland, Iceland, Norway, and Sweden	General Population	B	Age at initial census: 30-64	≈ 14.9 million	1960-1990	Occupation was 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	Kidney	National registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Calvert *et al.* (2011) [Brown and Kaplan, 1987; Ruder *et al.*, 1994; 2001]	US	NIOSH cohort of dry cleaners	B	Mean age at first employment: 34.5	1,704	–	Dry cleaning union records	Mort	Kidney	Death certificates and NDI	1940-2004
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	45,318 (5,443 exposed to TCE)	–	JEM	Mort	Kidney	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	Kidney	National cancer registry	1985-2006
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[b]	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	Kidney	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[b] CP: 34-60[b]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Kidney	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics facility workers	B	Mean age at hire: 25.7-28.7	34,494	1969-2001	Employment at the facility	Mort	Kidney	SSA, NDI, IRS, and death certificates	1969-2009

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
ATSDR (2018b)[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	Kidney	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	Mean age at entry: 36.7	5,369	–	Solvent exposure scores were calculated based on job titles from union records	Mort	Kidney	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; FIOH = Finnish Institute of Occupational Health; Inc = Incidence; IRS = Internal Revenue Service; JEM = Job Exposure Matrix; M = Males; Mort = Mortality; NCR = National Cancer Registry; NDI = National Death Index; NIOSH = National Institute for Occupational Safety and Health; NRCD = National Registry of the Cause of Death; PCE = Tetrachloroethylene; SSA = Social Security Administration; TCE = Trichloroethylene; U-TCA = Urinary Trichloroacetic Acid; 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) Ji *et al.* (2005) also reports results for total kidney cancer and renal pelvis cancer; however, these outcomes were better covered by Pukkala *et al.* (2009) and Wilson *et al.* (2008), respectively.

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

(c) 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, 2018b).

(d) Median age at survey or death (ATSDR, 2018b).

Table F.2 PCE and Kidney 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	3	3	1.06 (0.22-3.10)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	1.03 (0.21-3.01)		
Anttila *et al.* (1995)	Finland general population	Inc	SIR	Overall	2	–	1.82 (0.22-6.56)	–	Sex, age, and calendar yr
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**Persons Classified with Relevant Occupational or Industrial Code at Time of One or Both Censuses**					Sex, age, calendar period, geographic region, and urban setting
				Overall	121	–	1.11 (0.93-1.33)	–	
				Persons Classified with Relevant Occupational or Industrial Code at Time of Both Censuses					
				Overall	14	–	1.20 (0.71-2.02)	–	
				Female	11		1.59 (0.88-2.87)	0.12	
				Male	3		0.62 (0.20-1.93)		
Chang *et al.* (2003)	Taiwan general population	Mort	SMR	Male	0	1.31	–	–	Age, calendar yr, and sex
				Female	3	2.55	1.18 (0.24-3.44)		
				Duration of Employment (Yrs)					
				≤1	1	1.61	0.62	>0.05	
				>1 to 5	2	0.65	3.08		
				>5	0	0.28	–		
				Calendar-Yr Interval					
				1985-1990	0	0.65	–	>0.05	
				1991-1997	3	1.90	1.58		
Ji *et al.* (2005)	Other working persons in Sweden	Inc	SIR	**Launderers and Dry Cleaners**					Age, sex, calendar period, and SES
				Males in 1960 census	51	–	0.91 (0.68-1.17))	–	
				Females in 1970 census	79		**1.45 (1.15-1.79)**		
				Females in 1960 and 1970 censuses	21		1.61 (0.99-2.37)		
				Females in 1960, 1970, and 1980 censuses	1		0.59 (0.00-2.31)		
Sung *et al.* (2007)	Taiwanese general population	Inc	SIR	All female workers	15	13.6	1.10 (0.62-1.82)	–	Age and calendar yr

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
Wilson *et al.* (2008)	Swedish employed population	Inc	SIR	**Laundry Workers (Occupation)**					Age, sex, and calendar yr
				Female	5	–	1.23 (0.39-2.86)	–	
				Male	0		–		
				Laundering, Ironing, and Dyeing (Industry)					
				Female	8	–	1.45 (0.63-2.86)	–	
				Male	3		1.07 (0.21-3.12)		
Pukkala *et al.* (2009)	Employed population in Denmark, Finland, Iceland, Norway, and Sweden	Inc	SIR	Launderers (male)	62	–	0.89 (0.68-1.14)	–	Country, sex, age, and 5-yr calendar periods
				Launderers (female)	201		0.96 (0.84-1.10)		
Calvert *et al.* (2011)	US national population	Mort	SMR	Overall	5	–	1.14 (0.37-2.67)	–	Age, sex, race, and calendar time
				PCE-only (shop where PCE was the primary cleaning solvent)	2	–	1.35 (0.16-4.89)		
				PCE-plus (worked in PCE shops and shops mainly using other solvents)	3	–	1.04 (0.21-3.04)		
Lipworth *et al.* (2011)	California general population (white workers), US general population (non-white workers)	Mort	SMR	Factory workers exposed to PCE	13	16.3	0.80 (0.43-1.37)	–	Race, age, calendar yr, and sex
	Unexposed factory workers		RR	**Yrs Exposed**					Date of birth, date of hire, date of termination, sex, and race
				0	33	–	Ref.	>0.20	
				<1	1		0.18 (0.02-1.33)		
				1-4	5		0.83 (0.32-2.16)		
				≥5	6		0.95 (0.38-2.41)		
Seldén & Ahlborg Jr. (2011)	Swedish national population	Inc	SIR	Overall	29	–	1.04 (0.69-1.49)	–	Age, sex, and calendar yr
				Female	19		1.03 (0.62-1.60)		
				Male	10		1.06 (0.51-1.94)		
		Mort	HR	**CL Marines & Navy Personnel**					

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.* (2014a)	CP Marines & Navy personnel			*Cumulative exposure level (µg/L-months) with 10-yr lag*					Age, sex, race, rank, and education
				No/low (0-155)[b]	20	–	0.91 (0.46-1.78)	–	
				Medium/high (>155-8,585)[b]	22		1.55 (0.94-2.57)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-months[c]			Low (>1 -155)	8		1.40 (0.54-3.58)		
				Medium (>155-380)	11		1.82 (0.75-4.42)		
				High (>380-8,585)	11		1.59 (0.66-3.86)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Maximum cumulative exposure level (µg/L-mos) with 10-yr lag[c]					
				≥Median	7	0	∞	–	
Silver *et al.* (2014)	Workers of full risk set	Mort	HR	Cumulative PCE exposure	–	–	0.15 (0.1-4.04)	–	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	37	–	1.22 (0.86-1.68)	–	
				Females	6		1.07 (0.39-2.34)		
				Salaried Employees					
				Males	13	–	0.60 (0.32-1.03)	–	
				Females	0		0.00 (0.00-7.78)		
ATSDR (2018b)	CP Marine & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low (0-<36)	80	–	0.88 (0.55-1.41)	–	
				Medium (36-<711)	80		1.28 (0.79-2.05)		
				High (≥711)	32		1.79 (1.02-3.12)		
	CL Marines & Navy personnel with low exposure (>0-<36 µg/L-mos)[e]			Medium (36-<711)	80		**1.43 (1.02-2.00)**		
				High (≥711)	32		**2.01 (1.29-3.13)**		
	CP civilian employees			**CL Civilian Employees**					Age
				Cumulative exposure level (µg/L-mos)[d,f]					
				Low (<457)	3	–	0.34 (0.09-1.25)	–	
				Medium (457-<2,118)	8		1.80 (0.68-4.76)		
				High (≥2,118)	9		**13.92 (5.09-38.10)**		

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
	CL civilian employees with low exposure (<457 µg/L-mos)[e]			Medium (457-<2,118)	8		**5.34 (1.38-20.6)**		
				High (≥2,118)	9		41.54 (0.30-76.10)		
Callahan *et al.* (2019)	US general population	Mort	SMR	Overall	14	13	1.1 (0.6-1.9)	–	Age, sex, race, yr of enrollment in the union, and calendar period
				Yr Joined the Union					
				<1960	8	9	0.9 (0.4-1.7)	–	
				>1960	6	3	1.8 (0.7-3.9)		
	No/low exposure group		HR	**Level of Solvent Exposure**					Age, race, sex, and decade of enrollment
				10-yr lag					
				Medium	6	–	3.4 (0.6-18.6)	**0.004**	
				High	3		**17.8 (2.2-143.7)**		
				20-yr lag					
				Medium	6	–	4.1 (0.7-22.5)	**0.004**	
				High	3		**24.4 (2.9-201.6)**		
	Tertile 1			**Cumulative Estimated Solvent Exposure**					
				10-yr lag					
				Tertile 2	2	–	1.8 (0.2-20.8)	**0.03**	
				Tertile 3	8		6.6 (0.7-59.3)		
				20-yr lag					
				Tertile 2	2	–	2.0 (0.2-22.9)	**0.03**	
				Tertile 3	8		8.3 (0.9-75.8)		

ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; HRR = Hazard Rate Ratio; Inc = Incidence; Mort= Mortality; NR = None to Report; NYC = New York City; OR = Odds Ratio; PAHs = Polycyclic Aromatic Hydrocarbons; PCE = Tetrachloroethylene; Ref = Reference; RR = Relative Risk; SES = Socioeconomic Status; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SRR = Standardized Rate Ratio; SSFL = Santa Susana Field Laboratory; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compounds; US = United States; Yr(s) = Year(s).

– = 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.*, 2014a). I report the values consistent with the text definition.

(c) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al.*, 2014a,b).

(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 (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(e) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.
(f) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table F.3 PCE and Kidney 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	
Asal *et al.* (1988)	US	Inc	RCC	1981-1984	B	60	315	Hospitals	Hospital: 313 Population: 336	Hospitals and RDD	Self-reported occupation history
Aschengrau *et al.* (1993)	US	Inc	Kidney	1983-1986	B	–	35	Massachusetts Cancer registry	777	RDD, HCFA, and death certificates	Modeled dose based on residential history, distributions system, and pipe characteristics.[a]
McCredie and Stewart (1993)	Australia	Inc	RCC & CaRP	1989-1990	B	20-79	RCC: 489; CaRp: 147	New South Wales Central Cancer Registry	523	New South Wales electoral rolls	Self-reported occupational history
Aupérin *et al.* (1994)	France	Inc	RCC	1987-1991	B	–	196	Hospital	347	Hospitals	Self-reported occupational history
Mellemgaard *et al.* (1994)	Denmark	Inc	RCC	1989-1992	B	–	365	Cancer registry	396	Central population register	Self-reported employment in occupations, industries, and chemical exposures
Delahunt *et al.* (1995)	New Zealand	Inc	RCC	1978-1986	M	≥20	710	New Zealand Cancer registry	12,756	New Zealand Cancer registry	Cancer registry records of the current or most recent occupation at the time of registration
Mandel *et al.* (1995)	Australia US Denmark	Inc	Kidney	Unspecified	M	20-79	1732	National cancer registries	2309	Population-based electoral lists HCFA lists	Occupational industry/job titles collected by face-to-face interviews

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
	Sweden									Registers covering entire population	
	Germany							Clinical surveillance system		Residential lists	
Dosemeci *et al.* (1999)	US	Inc	RCC	1988-1990	B	20-85	438	MN Cancer Surveillance System	687	RDD and HCFA	Self-reported occupational history and JEM
Parent *et al.* (2000)	Canada	Inc	RCC	1979-1985	M	35-70	142	Hospital	Cancer: 1,900 Population: 533	Hospital (cancer controls) and RDD (population controls)	Self-reported *via* interview-style questionnaire
Pesch *et al.* (2000a)	Germany	Inc	RCC	1991-1995	B	Cases M: 69 F: 76 Controls M: 63 F: 67 (median)	935	Population-based enrollment, *via* large hospitals in the study areas	4,298	Local residency registries	Interview, self-reported job history, JEM
Brüning *et al.* (2003)	Germany	Inc	Kidney	1992-2000	B	Cases: 68 Controls: 66 (median)	134	Hospital records	401	Hospital records	Self-reported; occupational history linked to JEM and self-assessed exposure to PCE
Lynge *et al.* (2006)	Denmark, Finland, Norway, Sweden	Inc	Kidney	1970-2001	B	–	Total: 210 Men: 56 Women: 154	National population, death, and cancer registries	1,060	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	
Karami *et al.*, (2012b)	US	Inc	RCC, ccRCC	2002-2007 for Detroit; 2003 for Chicago	B	Mean: 59.9	1217	Metropolitan Detroit Cancer Surveillance System, and pathology reports in Chicago	1235	CMMS, and DMV records	Occupational history obtained from interviews
Christensen *et al.* (2013)	Canada	Inc	Kidney	1979-1985	M	35-70	177	Hospitals	Population: 442 Cancer: 1,594	Population-based electoral lists	Expert assessment of self-reported job history
Vlaanderen *et al.* (2013)	Finland, Iceland, Norway, Sweden	Inc	Kidney	1960-2005	B	30-64	76,130	All subjects who participated in the 1960, 1970, 1980-1981 and/or 1990 censuses	380,650	All subjects who participated in the 1960, 1970, 1980-1981 and/or 1990 censuses	JEM
Purdue *et al.* (2017)	US	Inc	Kidney	2002-2006 (white cases) 2002-2007 (black cases)	B	Cases: 20-64 Controls: 65-79	1,217	Metropolitan Detroit Cancer Surveillance System	1,235	DMV records and Medicare eligibility files	Occupational information self-reported *via* interview

Notes:
B = Both Males and Females; CaRP = Cancer of the Renal Pelvis; ccRCC = Clear Cell Renal Cell Carcinoma; CMMS =Centers for Medicare and Medicaid Services; DMV = Department of Motor Vehicles; HCFA = Health Care Finance Administration; Inc = ; JEM = Job-Exposure Matrix; M = Males; MN = Minnesota; PCE = Tetrachloroethylene; RCC = Renal Cell Carcinoma; RDD =Random Digit Dialing.
– = Not Reported.

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

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
Asal *et al.* (1988)	Inc	OR	**Employment in Dry Cleaning Industry**				–	Age, sex, smoking status, and weight
			Not employed in dry cleaning	–	–	Ref		
			Males	3	6	0.7 (0.2-2.3)		
			Females	8	1	2.8 (0.8-9.8)		
Aschengrau *et al.* (1993)	Inc	OR	**Adjusted, Without Latency**[a]				–	Sex; age at diagnosis (cases) or index yr (controls); vital status at interview; educational level; occupational exposure to PCE, benzene, and other solvents; smoking status; and previous urinary tract infection or kidney stones
			No exposure	–	–	Ref		
			Any PCE exposure	6	112	1.08 (0.42-2.79)		
			Any PCE exposure, mostly baths	–	–	3.23(0.54-19.17)		
			Low PCE exposure	6	101	1.36 (0.45-3.45)		
			High PCE exposure	0	11	–		
McCredie and Stewart (1993)	Inc	RR	**Employment in Dry Cleaning Industry**				–	Age, sex, method of interview, smoking status, and BMI
			Not employed in dry cleaning	–	–	Ref		
			RCC	16	7	2.49 (0.97-6.35)		
			CaRP	8	7	**4.68 (1.32-16.56)**		Age, sex, method of interview, smoking status, education, and use of phenacetin-containing analgesics
Aupérin *et al.* (1994)	Inc	–	Laundry workers	The authors stated that "the relative risks of renal cell carcinoma… among laundry workers could not be estimated in this study because the number of cases and controls… was too small."				
Mellemgaard *et al.* (1994)	Inc	OR	**Employment in Dry Cleaning Industry (≥1 Yr, with 10-Yr Lag)**				–	Age, sex, BMI, and smoking status
			Not employed in dry cleaning industry (≥1 yr)	–	–	Ref		
			Males	2	1	2.3 (0.2-27)		
			Females	2	1	2.9 (0.3-33)		
Delahunt *et al.* (1995)	Inc	RR	Non-dry cleaning occupation	–	–	Ref	–	Restricted to males and adjusted for age and smoking status
			Dry cleaning occupation	–	–	1.92 (0.27-13.89)		
	Inc	RR	**Industry or Occupation (≥1 Yr)**				–	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
Mandel *et al.* (1995)			Unexposed (<1 yr in industry or occupation)	–	–	Ref		Age group, sex, study center, education level, smoking status, BMI
			Dry-cleaning industry	8	12	0.9 (0.3-2.4)		
			Cutting oils or mist	168	191	1.2 (0.4-1.5)		
			Dry-cleaning solvents	245	223	**1.4 (1.1-1.7)**		
Dosemeci *et al.* (1999)	Inc	OR	Unexposed[b]	–	–	Ref	–	Restricted to white participants and adjusted for age, smoking status, hypertension status, use of diuretics, and/or use of anti-hypertension drugs, and BMI
			Overall	50		1.07 (0.7-1.6)		
			Males	42		1.12 (0.7-1.7)		
			Females	8		0.82 (0.3-2.1)		
Parent *et al.* (2000)	Inc	OR	Not laundry & cleaning workers	–	–	Ref	–	Respondent status (self *vs.* proxy), smoking, BMI
			Laundry & cleaning workers	4	–	1.7 (0.6-4.7)		
Pesch *et al.* (2000a)	Inc	OR	**RCC**					Age, study center, smoking status
			German JEM by PCE exposure index					
			Males					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	154		**1.4 (1.1-1.7)**		
			High	119		1.1 (0.9-1.4)		
			Substantial	50		1.4 (1.0-2.0)		
			Females					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	12		0.7 (0.4-1.3)		
			High	19		1.1 (0.7-1.9)		
			Substantial	4		0.7 (0.3-2.2)		
			JTEM by PCE exposure index					
			Males					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	44		1.2 (0.9-1.7)		
			High	39		1.1 (0.7-1.5)		
			Substantial	15		1.3 (0.7-2.3)		
			Females					
			Unexposed and low[c]	–	–	Ref	–	
			Medium	8		2.2 (0.9-5.2)		
			High	6		1.5 (0.6-3.8)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Substantial	3		2.0 (0.5-7.8)		
Brüning *et al.* (2003)	Inc	OR	**Self-Reported Exposure to PCE**				–	Age, sex, and smoking
			Never exposed	–	–	Ref		
			Ever exposed	7	12	1.64 (0.61-4.40)		
			Duration of Exposure (Yrs)					
			No Exposure	127	389	Ref		
			<10	4	6	2.46 (0.65-9.34)		
			≥10	3	7	1.02 (0.24-4.27)		
Lynge *et al.* (2006)	Inc	RR	**Dry Cleaners, Owners of Dry-Cleaning Shops, and Other Persons Employed in Dry-Cleaning Shops with <10 Workers**					Alcohol consumption, smoking status, country, sex, age group, and calendar period
			Unexposed	129	589	Ref	–	
			Overall	29	196	0.67 (0.43-1.05		
			Employment duration (yrs)					
			Unexposed	125	505	Ref	–	
			0-1	1	12	0.24 (0.03-2.04)		
			2-4	4	19	0.86 (0.28-2.67)		
			5-9	8	47	0.70 (0.32-1.55)		
			≥10	14	71	0.75 (0.39-1.42)		
			Unknown	2	11	0.70 (0.15-3.36)		
Karami *et al.* (2012b)	Inc	OR	**RCC, by Duration in Industry or Occupation (Yrs)**					Sex, age at reference date, race, study center, education level, history of hypertension, smoking status, BMI (5 yrs prior to interview) and family history of cancer
			Laundering and dry-cleaning machine operators and tenders					
			Never	1,177	1,202	Ref	0.997	
			Ever	7	9	0.8 (0.3-2.3)		
			<5	4	6	0.6 (0.1-2.4)		
			≥5	3	3	1.2 (0.2-8.7)		
			Dry-cleaning plants, except rug					
			Never	1,169	1,198	Ref	0.093	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Ever	15	13	2.0 (0.9-4.4)		
			<5	11	10	1.8 (0.6-5.4)		
			≥5	4	3	2.5 (0.4-14.4)		
			ccRCC, by Duration in Industry or Occupation (Yrs)					
			Dry cleaning plants, except rug					
			Never	677	1198	Ref	**0.031**	
			Ever	13	13	**3.0 (1.2-7.4)**		
			<5	10	10	2.9 (0.9-9.1)		
			≥5	3	3	3.7 (0.6-25.4)		
Christensen *et al.* (2013)	Inc	OR	Never exposed to chlorinated solvents	134	403 population, 1,497 cancer	Ref	–	Smoking status; age; income; level of education; ethnicity; questionnaire type (self-reported *vs.* proxy); and coffee, beer, wine, and spirit intake
			Any PCE exposure	2	4 population, 31 cancer	1.0 (0.2-4.5)		
			Substantial PCE exposure	2	2 population, 20 cancer	1.6 (0.3-8.1)		
Vlaanderen *et al.* (2013)	Inc	HR	**Tertiles of Cumulative PCE Exposure**					Age, country, and sex
			Unexposed	–	–	Ref	–	
			First	375		1.11 (0.99-1.24)		
			Second	333		0.96 (0.86-1.08)		
			Third	314		0.94 (0.86-1.06)		
Purdue *et al.* (2017)	Inc	OR	**Exposure Probability**					Age, sex, race, study center, education level, smoking status, BMI, and history of hypertension
			Unexposed	652	705	Ref	–	
			<50%	499	469	1.1 (0.9-1.4)		
			50%-89%	17	21	0.9 (0.4-1.9)		
			≥90	22	16	1.2 (0.6-2.3)		
			Any Exposure Intensity (≥50% Exposure Probability)					
			Duration (yrs)					
			Unexposed	652	705	Ref	0.77	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			1-3	13	12	1.1 (0.4-2.9)		
			4-9	13	14	1 (0.4-2.5)		
			≥10	13	11	1.1 (0.5-2.5)		
			Average weekly exposure (hrs)					
			Unexposed	652	705	Ref	0.83	
			≤1	18	15	1 (0.5-2)		
			>1-15	10	7	1.1 (0.5-4.1)		
			>15	11	14	1.1 (0.4-3.1)		
			Cumulative (hrs)					
			Unexposed	652	705	Ref	0.95	
			Tertile 1 (≤936)	16	12	1.2 (0.5-2.8)		
			Tertile 2 (937-4,680)	15	13	1.1 (0.6-2.1)		
			Tertile 3 (>4,680)	8	11	0.9 (0.3-3.3)		
			High-Intensity Exposure					
			Duration (yrs)					
			Unexposed	652	705	Ref	0.78	
			1-3	10	10	0.9 (0.3-2.6)		
			4-9	11	8	1.4 (0.5-4)		
			≥10	13	8	1.4 (0.6-3.4)		
			Average weekly exposure (hrs)					
			Unexposed	652	705	Ref	0.15	
			≤1	18	13	1.1 (0.5-2.3)		
			>1-15	9	7	1.2 (0.4-3.7)		
			>15	7	5	2.5 (0.6-10.6)		
			Cumulative (hrs)					
			Unexposed	652	705	Ref	**0.03**	
			Tertile 1 (≤624)	13	9	1.4 (0.5-3.8)		
			Tertile 2 (625-1,820)	7	8	0.5 (0.2-1.4)		
			Tertile 3 (>1,820)	14	8	**3.1 (1.3-7.4)**		

Notes:
BMI = Body Mass Index; CaRP = Cancer of the Renal Pelvis; ccRCC = Clear Cell Renal Cell Carcinoma; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; OR = Odds Ratio; PCE = Perchloroethylene; RCC = Renal Cell Carcinoma; Ref. = Reference; RR = Relative Risk; Yr(s) = Years(s).
– = Not Reported.
Bolded values indicate statistical significance.
(a) Aschengrau *et al*. (1993) reported no cases when considering latency.

(b) Dosemeci *et al*. (1999) did not clearly define the reference population. I generally considered it unexposed, but it was not clear if the reference group was individuals unexposed to all chemicals considered across all analyses or unexposed to the specific chemical of interest in each individual analysis.
(c) Pesch *et al*. (2000a) 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."

Attachment G

PCE Animal Carcinogenicity Studies

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

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

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

Table G.4 PCE and Kidney Cancer Chronic Toxicity Study Quality Assessment

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

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period	Treatment Groups (n, sex)	Dose (mg/kg-day)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
NCI (1977)[a, b]	Osborne-Mendel rats	78	110 weeks	20 M	0	1/20	3/20
				50 M	471	0/49	1/49
					941	1/50	0/50
				20 F	0	0/20	0/20
				50 F	474	0/50	0/50
					949	0/50	1/50
	B6C3F1 mice		90 weeks	20 M	0	0/20	0/20
				50 M	536	0/49	1/49
					1,072	0/48	0/48
				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.
(a) Following exposure, rats and mice were observed for 32 and 12 weeks, respectively. Regarding results in rats, 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." Regarding results in mice, NCI (1977) concluded: "No significant differences were observed."
(b) In NCI (1977), I used the number of animals necropsied when the denominators for incidences were not specified.

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

Citation	Strain/Species	Exposure Duration (weeks)	Observation Period	Treatment Groups (n, sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
NTP (1986a)[a, b]	F344/N rats	104	112-113 weeks	50 M	0	1/49	0/49
					200	4/49	1/49
					400	2/50	2/50
				50 F	0	0/50	0/50
					200	0/50	0/50
					400	0/50	0/50
	$B6C3F_1$ mice			50 M	0	0/49	0/49
					100	0/49	1/49
					200	0/50	0/50
				50 F	0	0/49	0/49
					100	0/50	0/50
					200	0/50	0/50
JISA (1993)	Fischer rats	104	110-111 weeks	50 M	0	1/50	0/50
					50	2/50	0/50
					200	1/50	0/50
					600	2/50	1/50
				50 F	0	1/50	0/50
					50	0/50	0/50
					200	0/50	0/50
					600	0/50	1/50
	$Crj:BDF_1$ mice			50 M	0	0/50	0/50
					10	1/50	0/50
					50	0/50	1/50
					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; M = Male; NR = Kidney was analyzed, but kidney tumor findings were not reported; ppm = Parts Per Million.
(a) NTP (1986a) 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.
(b) In NTP (1986a), I used the number of animals necropsied when the denominators for incidences were not specified.

Table G.3 PCE and Kidney 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 in two out of the three chronic studies with the exception of NCI (1977).
Bias	Potential bias was identified in the chronic studies of PCE. 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 (1986a) and JISA (1993) chronic inhalation studies. NTP (1986a) 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 (1986a) reported that in several instances rats and mice escaped from their cages within the exposure chambers. ATSDR (2019b) 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. Therefore, the study may have been impacted by the reduced survival in the treatment groups.
Sample	The chronic studies had adequate sample sizes, except for NCI (1977). The number of animals in the control groups (n = 20) for rats and mice were significantly less than the number of animals in the exposure groups (n = 50).
Chemical Administration and Characterization	All chronic studies provided adequate information on chemical source, purity, or composition, and independently verified chemical purity or took steps to ensure reported exposure levels were accurate.
Exposure Conditions	Exposure duration was too short (78 weeks) to assess carcinogenicity in rats (NCI, 1977). Two chronic studies (NTP, 1986a; 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, 1986a; JISA, 1993) had observation periods that were too long (110-113 weeks).

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; JISA = Japan Industrial Safety Association; NCI = National Cancer Institute; NTP = National Toxicology Program; PCE = Perchloroethylene.

Table G.4 PCE and Kidney Cancer Chronic Toxicity 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 (1986a)	**Reporting** **Allocation** **Sample** **Chemical Administration and Characterization** **Exposure Conditions** (rats)	**Bias:** Reduced survival potentially attributable to tumors (but not kidney 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 potentially attributable to tumors (but not kidney tumors); 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 Kidney Cancer Case-Control Study Characteristics

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Table H.5 Benzene and Kidney Cancer Meta-Analysis Results

Table H.1 Benzene and Kidney 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
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	Kidney	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	Kidney	Death certificates	1942-1980
Dagg *et al.* (1992) [Wong *et al.*, 1986]	US	Oil refinery employees	M	$\bar{x}$ = 27.3 (range = 11.8-79)	13,397	1950-1986	Work histories	Mort	Kidney	Company records, NDI, SSA, California Death Index, Equifax[a], and death certificates	1950-1986
Rushton (1993)[b]	UK	Oil refinery and petroleum distribution workers	M	–	Refinery workers: 34,569 Distribution center workers: 23,306	1950-1975	Work histories	Mort	Kidney	National Health Service Central Register and death certificates	1976-1989
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	Kidney	Company records, NDI, and SSA Master Beneficiary Record file	1973-1989

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
Wong *et al.* (1993)	US	Petroleum marketing/ distribution workers	B	–	18,135	1946-1985	Employment records, work histories, and JEM based on hydrocarbon measurements	Mort	Kidney	SSA, Death Master File, NDI, company records, state vital statistics departments, and death certificates	1947-1989
Honda *et al.* (1995) [Wongsrichanalai *et al.*, 1989]	US	White male workers at a petroleum manufacturing plant	M	–	9,796	1940-1989	Employment at the petroleum manufacturing plant	Mort	Kidney	Company records, SSA Death Master file, NDI, state DMVs, and death certificates	1940-1989 (salaried) 1942-1989 (hourly)
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	Kidney	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	Kidney	Personnel annuitant records, DMV, SSA, and NDI	1937-1987
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	Kidney	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

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
Pukkala (1998)	Finland	Oil and chemical enterprise employees[c]	B	Median <30	Total: 9,454 M: 7,512 F: 1,942	1967-1982	Employment at the company/ enterprise	Inc	Kidney	Finnish Cancer Registry	1971-1994
Bulbulyan *et al.* (1999)	Russia	Printing plant employees	F	–	3,473	Minimum 2 yrs of employ-ment at baseline: 1979[d]	Personnel records and job group	Mort	Kidney	Death certificates from Moscow Vital Statistics Department	1979-1993
Consonni *et al.* (1999) [Bertazzi *et al.*, 1989	Italy	Oil refinery workers	M	–	1,583	1949-1982	Work history records	Mort	Kidney	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, F: 2,093	1947-1977	Personnel separation rosters and complete work histories	Mort	Kidney	Company files, NDI, SSA, HCFA, and death certificates	1947-1993
Lewis *et al.* (2000a)[e] [Hanis *et al.*, 1985a,b; Shallenberger *et al.*, 1992; 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	Kidney	Company records, NDI, SSA, and death certificates	1970-1992

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
Wong *et al.* (2001a)	US	Oil refinery employees	B	–	Total: 3,328 M: 2,965 F: 363	1959-1997	Personnel records and payroll files	Mort	Kidney	Company records, 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	1945-1996	Personnel records and payroll files	Mort	Kidney	Company records, PBI, SSA Death Master File, NDI/NDI Plus, and death certificates	1946-1996
Sorahan *et al.* (2002)[b]	UK	Oil refinery and petroleum distribution workers	M	<85	Total: 45,110 Refinery workers: 28,690 Distribution workers: 16,480	1946-1974	Work histories	Mort	Kidney	NHS Central Register, General Register Office for Scotland, and death certificates	1951-1998
Lewis *et al.* (2003) [Lewis *et al.*, 2000b; Schnatter *et al.*, 1993; 1992]	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	Company's personnel, payroll, and HR databases	Inc & mort	Kidney	Cases: Canadian Cancer Data Base Deaths: Canadian Mortality Data Base	Inc: 1969-1994 Mort: 1964-1994
Tsai *et al.* (2003)	US	Chemical and refinery facility workers	M	Baseline $\bar{x}$ = 34.2	3,579	1973-1999	Shell Health Surveillance System and work history data	Mort	Kidney	Company records, NDI, and SSA Master Beneficiary Record file	1973-1999

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
Huebner *et al.* (2004)[e] [Hanis *et al.*, 1985a,b; Shallenberger *et al.*, 1992; Gamble *et al.*, 2000]	US	Oil refinery and petrochemical employees	M	$\bar{x}$ = 27 (includes F)	13,182	1970-1982	Health status registry of work history records, and paperwork records	Mort	Kidney	Benefits records, NDI, SSA, and death certificates	1970-1997
Sorahan *et al.* (2005)	UK	Benzene workers	B	<85	5,514	–	Personnel reports	Inc & Mort	Kidney	ONS and DHSS	1968-2002 (mortality); 1971-2001 (incidence)
Gun *et al.* (2006)	Australia	Employees of Australian Institute of Petroleum member companies[f]	M	Median = 55	16,547	1980-2000	Survey interviews; exposure ranking by industrial hygienists based on job code	Inc & Mort	Kidney	NDI and National Cancer Statistics Clearing House	Incidence: 1981-2000 Mortality: 1980-2001
Tsai *et al.* (2007) [Tsai *et al.*, 1996]	US	Petroleum refinery and chemical workers	M	–	9,764	1948-2003	Shell Health Surveillance System and work history data	Mort	Kidney	Company records, NDI, and SSA Master Beneficiary Record file	1948-2003
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[g]	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	Kidney	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
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[g] CP: 34-60[g]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Kidney	SSA and NDI	1979-2008
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	Kidney	HR records, NDI, state vital statistics bureaus, death certificates	1940-2009
ATSDR (2018b)[h]	US	Marines and Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[i] Civilian Employees CL: 60-64[i] CP: ≥65[i]	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 (Marine and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Kidney	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; F = Females; HCFA = United States Health Care Financing Administration; HR = Human Resources; Inc = Incidence; JEM = Job-Exposure Matrix; M = Males; $\bar{x}$ = Mean; Mort = Mortality; NDI = National Death Index; ONS = Office for National Statistics; PBI = Pension Benefits Information; SSA = Social Security Administration; UK = United Kingdom; US = United States; yrs = Years.
– = 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) Rushton (1993) and Sorahan *et al.* (2002) evaluate the same population. I report results from Sorahan *et al.* (2002) overall because it has a longer follow-up and report results by duration of exposure from Rushton (1993).
(c) Includes employees in clerical, technical, and blue-collar positions (Pukkala, 1998).
(d) Benzene was used in book binding processes in these plants till 1958 (Bulbulyan *et al*., 1999).
(e) 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).
(f) Head office staff and those at facilities with less than 10 employees were excluded (Gun *et al.,* 2006).
(g) Median age from start to end of follow-up (Bove *et al.*, 2014a,b).
(h) 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, 2018b).
(i) Median age at survey or death (ATSDR, 2018b).

Table H.2 Benzene and Kidney 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}	Covariates Controlled For
Wong (1987a, b)[b]	US general population	Mort	SMR	**Continuously Exposed Workers**				–	Age, sex, race, and calendar time
				All	4	2.86	1.40 (0.38-3.58)		
				Duration of exposure (yrs)					
				<5	3	–	1.84		
				5-14	0		0		
				≥15	1		1.83		
				Cumulative exposure (ppm-mos)					
				<180	2	–	1.51		
				180-719	2		2.45		
				≥720	0		0		
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	3	3	1.06 (0.22-3.10)	–	Age, calendar time, sex, and race
				Non-inspectors	3	3	1.03 (0.21-3.01)		
Dagg *et al.* (1992)	US general population	Mort	SMR	**Work Location**					Age, sex, race, and calendar period
				Richmond	13	–	1.01 (0.54-1.73)	–	
				El Segundo	3		0.41 (0.09-1.20)		
				Overall	17		0.84 (0.49-1.34)		
				Duration of Employment (Yrs):					
				Richmond oil refinery					
				<5	3	–	2.39 (0.49-6.99)	–	
				5-14	2		0.76 (0.09-2.76)		
				15-29	2		0.46 (0.06-1.65)		
				≥30	6		1.30 (0.48-2.83)		
				El Segundo oil refinery					
				<5	0	–	– (0-3.86)	–	
				5-14	0		– (0-2.67)		
				15-29	1		0.38 (0.01-2.12)		
				≥30	2		0.85 (0.10-3.06)		
				Time Since Hire (Yrs)					
				Richmond oil refinery					
				<10	0	–	– (0-7.16)	–	
				10-19	2		1.26 (0.15-4.56)		
				20-29	0		– (0-1.12)		
				≥30	11		1.47 (0.73-2.63)		
				El Segundo oil refinery					

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				<10	0	–	– (0-11.75)	–	
				10-19	1		1.08 (0.03-6.01)		
				20-29	0		– (0-1.95)		
				≥30	2		0.48 (0.06-1.73)		
				Hire Date					
				Richmond oil refinery					
				≤1948	9	–	0.88 (0.40-1.67)	–	
				>1948	4		1.52 (0.41-3.89)		
				El Segundo oil refinery					
				≤1948	3	–	0.53 (0.11-1.55)	–	
				>1948	0		– (–)		
Rushton (1993)[c]	England, Wales, or Scotland general populations	Mort	SMR	Refinery workers	56	55.3	1.01 (0.77-1.32)	–	Age, sex, and calendar period
	England and Wales general populations			Distribution center workers	53	43.8	1.21 (0.91-1.58)		
				All drivers	25	17.7	1.41 (0.91-2.08)		
				Company of Employment for Petroleum Distribution Workers					
				Company 1	2	3.3	0.61 (0.07-2.21)	–	
				Company 2	35	27.8	1.26 (0.88-1.75)		
				Company 3	16	12.8	1.25 (0.72-2.04)		
				Yrs Since First Exposure					
				0-9	2	2.2	0.90 (0.11-3.25)	–	
				10-19	7	6.6	1.06 (0.43-2.19)		
				20-29	8	10.6	0.75 (0.33-1.49)		
				30-39	20	11.1	**1.80 (1.10-2.79)**		
				40-49	10	7.6	1.32 (0.63-2.43)		
				50+	6	5.7	1.05 (0.38-2.28)		
Tsai *et al.* (1993)	California general population	Mort	SMR	**Location**					Age, sex, race, and calendar period
				Martinez location	2	–	0.62 (0.07-2.22)	–	
				Wilmington location	6		2.16 (0.79-4.71)		
				Locations combined	8		1.33 (0.57-2.62)		
Wong *et al.* (1993)	US general population	Mort	SMR	All employees	24	–	0.740	–	Age, sex, race, and calendar period
				Land-Based Terminal Employees					

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				All workers	12	–	0.654 (0.337-1.141)	–	
				Length of exposure (yrs)					
				1-4	0	–	–	–	
				5-9	0		–		
				10-19	6		1.460		
				20-29	3		0.469		
				30+	3		0.608		
				Time since first exposure (yrs)					
				<10	0	–	–	–	
				10-19	3		1.196		
				20-29	3		0.753		
				30+	6		0.554		
				Job category					
				Driver only	2	–	0.451	–	
				Operator only	1		0.622		
				Other terminal jobs only	1		0.713		
				Cumulative exposure (ppm-yrs)					
				<500	4	–	1.187	–	
				500-1000	1		0.395		
				1000-2000	4		0.947		
				2000+	3		0.365		
				Cumulative frequency of peak exposure					
				<100	2	–	0.580	–	
				100-500	1		0.487		
				500-3000	5		0.976		
				>3000	4		0.484		
				Marine Employees					
				All workers	12	–	0.837 (0.458-1.405)	–	
				Length of exposure (yrs)					
				1-4	6	–	0.735	–	
				5-9	3		0.945		
				10-19	3		1.208		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				20-29	0		–		
				30+	0		–		
				Time since first exposure (yrs)					
				<10	0	–	–	–	
				10-19	3		1.068		
				20-29	4		1.004		
				30+	5		0.762		
				Job Category					
				Deck only	5	–	1.244	–	
				Nondeck only	4		0.723		
Honda *et al.* (1995)	US white male population	Mort	SMR	Overall[d]	23	–	0.97 (0.61-1.45)	–	Age, sex, race, and calendar period
				Ever hourly	21		1.04 (0.64-1.58)		
Collingwood *et al.* (1996)	US general population	Mort	SMR	Overall	4	9.1	0.44 (0.12-1.12)	–	Age, sex, race, and calendar period
				White Males					
				All	4	8.4	0.48 (0.12-1.22)	–	
				Duration employment (yrs)					
				<20	0	–	0 (–)	–	
				20-29	3		1.45 (0.30-4.23)		
				30+	1		0.24 (0.01-1.32)		
				Time since first employment (yrs)					
				<20	0	–	0 (–)	–	
				20-29	2		1.27 (0.15-4.59)		
				30+	2		0.33 (0.04-1.20)		
Satin *et al.* (1996)	US general population	Mort	SMR	Overall	40	32.7	1.224 (0.875-1.667)	–	Age
	Texas general population					31.3	1.279 (0.914-1.742)		
				Race and Sex					
				White men	27	–	1.072 (0.707-1.560)	–	
				Non-white men	10		2.021 (0.969-3.717)		
				White women	3		2.775 (0.573-8.109)		
				Length of Employment (Yrs)					

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				<1	9	–	1.479 (–)	–	
				1-9	6		1.151 (–)		
				10-19	4		1.102 (–)		
				20-29	7		1.342 (–)		
				30+	14		1.259 (–)		
				Yrs Since Hired					
				<10	1	–	1.281 (–)	–	
				10-19	4		1.608 (–)		
				20-29	7		1.086 (–)		
				30-39	14		1.373 (–)		
				40+	14		1.232 (–)		
				Period of Hire					
				<1940	16	–	1.027 (–)	–	
				1940-1945	12		1.159 (–)		
				>1945	12		2.251 (–)		
				Pay Status					
				Hourly	36	–	1.381 (–)	–	
				25-75% Salaried	3		1.331 (–)		
				90-100% Salaried	1		0.362 (–)		
Lynge *et al.* (1997)	Danish, Finnish, Norwegian, and Swedish general populations	Inc	SIR	**Service Station Workers in Nordic Countries**					Age and sex
				Males	53	40.46	1.3 (1.0-1.7)	–	
				Females	4	3.44	1.2 (0.3-3.0)		
Pukkala (1998)	Finish general population	Inc	SIR	All employees	26	13	**1.97 (1.29-2.88)**	–	Age and calendar period
				Males					Age, sex, and calendar period
				All	25	–	**2.13 (1.38-3.13)**	–	
				Duration of employment (yrs)[e]					
				<5	4	2.5	1.58 (0.43-2.05)	–	
				≥5	15	5.2	**2.87 (1.61-4.73)**		
				Yrs after first known employment					
				5-14	12	–	**2.61 (1.35-4.56)**	–	
				Type of work[f]					
				Blue-collar	18	–	**2.31 (1.37-3.64)**	–	
				Technical	5		2.40 (0.78-5.60)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				Clerical	12		**2.51 (1.30-4.38)**		
				Location of work[f]					
				Porvoo oil refinery	12	–	**2.51 (1.30-4.39)**	–	
				Naantali oil refinery	7		2.32 (0.93-4.78)		
				Chemicals	2		1.84		
				Head office	3		1.79		
				Unknown	4		1.48		
				Type of oil refinery work[f]					
				Technical/clerical	14	–	**3.13 (1.66-5.34)**	–	
				Blue-collar	12		**2.41 (1.25-4.22)**		
Bulbulyan *et al.* (1999)	Moscow general population (1992 rates)	Mort	SMR	All printing plant employees	6	4.2	1.4 (0.5-3.1)	–	Age and sex
				Compositors	2	0.5	4.4 (0.5-15.7)		
				Press operators	1	0.6	–		
				Bookbinders	3[g]	1.6	1.9 (0.4-5.6)		
Consonni *et al.* (1999)	Italian general (1949-1968) and Lombardy Region populations (1969-1991)	Mort	SMR	All workers	3	2.7	1.10 (0.22-3.20)	–	Age, sex, and calendar year
				Length of Employment (Yrs), 10 Yr Lag					
				0-4	1	0.6	1.77 (0.02-9.85)	–	
				5-14	1	1.0	0.97 (0.01-5.38)		
				15+	1	1.1	0.88 (0.01-4.89)		
				Time Since First Employment (Yrs)					
				0-9	0	0.2	0 (0-23.82)	–	
				10-19	1	0.5	2.10 (0.03-11.66)		
				20-29	2	1.0	1.96 (0.22-7.09)		
				30+	0	1.1	0 (0-3.37)		
Divine *et al.* (1999)	US general population	Mort	SMR	**Demographic Group**					Age, sex, and race
				White men	55	–	0.94 (0.71-1.22)	–	
				Non-white men	1		0.53 (0.01-2.93)		
				Women	1		0.65 (0.01-3.60)		
				White Men					
				Duration of employment (yrs)					
				<10	3	–	0.73 (0.15-2.14)	–	
				10-19	8		0.98 (0.42-1.92)		
				20-29	18		1.17 (0.69-1.85)		
				>30	26		0.84 (0.55-1.23)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				Period of employment					
				<1950	43	–	0.94 (0.68-1.26)	–	
				>1950	12		0.94 (0.49-1.64)		
				Job and process unit employed >5 yrs					
				Office; professional; supervisor	15	–	0.80 (0.45-1.31)	–	
				Controlmen; operators	26		1.10 (0.72-1.61)		
				Craft; maintenance	22		1.05 (0.66-1.59)		
				Laboratory	1		**0.16 (0-0.89)**		
				Fluid catalytic cracking	7		1.93 (0.77-3.98)		
				Pipefitter; boilermaker	7		1.27 (0.51-2.61)		
				Crude stills	7		1.54 (0.62-3.17)		
				Motor oil	2		0.98 (0.11-3.52)		
Lewis *et al.* (2000a)[h]	US male general population	Mort	SMR	All facilities		24.3	**1.44 (1.00-2.00)**	–	Age, sex, race, and calendar year
				Bayway, NJ facility	7	5.4	1.29 (0.52-2.65)	–	
Wong *et al.* (2001a)	US general population	Mort	SMR	Total cohort	3	4.79	0.627 (0.129-1.832)	–	Age, sex, race, and calendar year
				Males					
				All	3	4.70	0.638 (0.132-1.865)	–	
				Duration of employment (yrs)					
				<10	1	–	0.959	–	
				10-29	2		0.742		
				30+	0		0.0		
				Time since first employment (yrs)					
				<20	2	–	2.869	–	
				20-39	1		0.411		
				40+	0		0.0		
				Job category					
				Maintenance	1	1.79	0.557 (0.014-3.106)	–	
				Process	2	1.51	1.327 (0.161-4.795)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Wong *et al.* (2001b)	US general population	Mort	SMR	All employees	16	17.09	0.936 (0.535-1.521)	–	Age, sex, race, and calendar yr
				Female employees	0	0.47	0.0 (0.0-7.781)		
				Males Employees					
				All	16	16.61	0.963 (0.550-1.564)	–	
				Time since first employment (yrs)					
				<20	0	–	0.0	–	
				20-39	7		0.969		
				40+	9		1.174		
				Duration of employment (yrs)					
				<10	4	–	1.739	–	
				10-29	5		0.943		
				30+	7		0.777		
				Maintenance employees					
				<10	1	–	0.379	–	
				10-29	4		1.098		
				30+	3		1.168		
				Overall	8		0.904		
				Process employees					
				<10	1	–	0.481	–	
				10-29	3		0.990		
				30+	0		0.0		
				Overall	4		0.600		
Sorahan *et al.* (2002)[c]	UK general population	Mort	SMR	Refinery workers	66	60.2	1.10 (0.85-1.39)	–	Age and sex
				Petroleum distribution workers	45	37.5	1.20 (0.88-1.61)		
Lewis *et al.* (2003)	Canadian general population	Inc	SIR	Males	15	15.01	1.00 (0.56-1.65)	–	Age, sex, and calendar period
				Females	2	3.49	–[i]		
				Duration of Employment, Males (Yrs)					
				<10	5	6.17	0.81 (0.26-1.89)	–	
				≥10-<20	7	3.87	1.81 (0.73-3.72)		
				≥20	1	1.43	–[i]		
		Mort	SMR	Males	3	4.79			
				Females	1	0.92			

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Tsai *et al.* (2003)	US general population	Mort	SMR	**Male Employees**					Age, sex, race, and calendar time
				All	6	4.6	1.31 (0.48-2.85)	–	
				≥10 yrs of employment	5	4.3	1.17 (–)	–	
	Louisiana general population					4.7	1.06 (–)		
	Industrial corridor general population					4.7	1.07 (–)		
Huebner *et al.* (2004)[h]	Louisiana and Texas general populations	Mort	SMR	**Work Location**					Age, sex, race, and calendar period
				Baton Rouge	21	14.43	1.46 (0.90-2.22)	–	
				Baytown	15	13.30	1.13 (0.63-1.86)		
				Hired <1950					
				Baton Rouge	17	10.99	1.55 (0.90-2.48)	–	
				Baytown	13	10.26	1.27 (0.68-2.17)		
				Hired ≥1950					
				Baton Rouge	4	3.44	1.16 (0.32-2.98)	–	
				Baytown	2	3.04	0.66 (0.08-2.38)		
				Duration of Employment (Yrs) (≥20 Yrs between First Employment and Death)					
				Baton Rouge					
				<15	0	0.47	–	–	
				15-29	7	3.51	2.00 (0.80-4.11)		
				30+	13	9.12	1.43 (0.76-2.44)		
				Baytown					
				<15	0	0.50	–	–	
				15-29	3	3.43	0.87 (0.18-2.56)		
				30+	11	7.98	1.38 (0.69-2.47)		
				Hired <1950: Baton Rouge					
				<1940	2	2.86	–	–	
				1940-1944	9	5.45	1.65 (0.76-3.14)		
				1945-1949	6	2.68	2.23 (0.82-4.86)		
Sorahan *et al.* (2005)	England and Wales general population	Mort	SMR	Exposed workers	14	13.6	1.03 (0.56-1.73)	–	Age, sex, and calendar year
		Inc	SIR	Exposed workers	16	17.8	0.90 (0.51-1.46)		
Gun *et al.* (2006)	Australian general population	Inc	SIR	All male workers	45	39.1	1.15 (0.84-1.54)	–	Age, sex, and calendar period
				Tanker drivers	12	5.84	**2.05 (1.06-3.59)**		
		Mort	SMR	All male workers	14	14.7	0.95 (0.52-1.60)		
		Mort	SMR	**Work Location**					

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Tsai *et al.* (2007)	County general population			Refinery	14	–	0.84 (0.46-1.42)	–	Age, sex, race, and time period
				Chemical	7		0.60 (0.24-1.24)		
				Total	21		0.74 (0.46-1.14)		
				Period of Hire					
				<1950	13	–	0.79 (0.42-1.35)	–	
				1950-1959	6		0.72 (0.27-1.57)		
				≥1960	2		0.58 (0.07-2.11)		
				Worked for ≥10 Years, by Work Location					
				Refinery	13	–	1.09 (0.58-1.86)	–	
				Chemical	4		0.56 (0.15-1.43)		
				Total	17		0.89 (0.52-1.42)		
Bove *et al.* (2014a)	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)[j]	22	–	1.03 (0.54-1.94)	–	
				Medium/high (>45-601)[j]	20		1.48 (0.88-2.47)		
	CL Marines & Navy personnel with exposure <2 µg/L-mos[k]			Low (2-45)	8		1.31 (0.52-3.29)		
				Medium (>45-110)	10		1.38 (0.58-3.28)		
				High (>110-601)	10		1.36 (0.57-3.25)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median[j]	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Maximum cumulative exposure level with 10-yr lag[k]					
				≥Median	5	–	1.82 (0.34-9.78)	–	
Collins *et al.* (2015)	US general population	Mort	SMR	Overall	8	–	0.78 (0.34-1.55)	–	Age, sex, race, and year
				>30-yrs since first benzene exposure	6		0.80 (0.29-1.74)		
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level[l,m]					
				Low	82	–	0.90 (0.56-1.45)	–	
				Medium	86		1.33 (0.84-2.13)		
				High	24		1.42 (0.78-2.58)		
	CL Marines & Navy personnel with low exposure[n]			Medium	86		**1.45 (1.05-2.00)**		
				High	24		1.55 (0.95-2.54)		

Notes for Table H.2:
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; ppm = parts per million; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; TX = Texas; 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 kidney 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) Rushton (1993) and Sorahan *et al.* (2002) evaluate the same population. I report results from Sorahan *et al.* (2002) overall because it has a longer follow-up and report results by duration of exposure from Rushton (1993).
(d) Included salaried workers who had a longer follow-up time than hourly workers (Honda *et al.,* 1995).
(e) Duration of employment data includes only oil refinery workers (Pukkala, 1998).
(f) Numbers do not add to the total number of male employees (Pukkala, 1998).
(g) Occurred exclusively among bookbinders hired prior to 1958 (Bulbulyan *et al*., 1999).
(h) 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).
(i) Unless the SMR was statistically significant when the number of cases/deaths <5, the SIR/SMR and 95% CI were not presented (Lewis *et al.,* 2003).
(j) 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*., 2014a). I report the values consistent with the text definition.
(k) To evaluate exposure-response relationship the authors also evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al*., 2014a,b).
(l) 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).
(m) 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, 2018b).
(n) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

Table H.3 Benzene and Kidney Cancer Case-Control Study Characteristics

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Years)	Cases		Controls		
							N	Source	N	Source	
McCredie and Stewart (1993)	Australia	Inc	RCC, CaRP	1989-1990	B	20-79	RCC: 489 CaRP: 147	New South Wales Central Cancer Registry	523	New South Wales electoral rolls	Self-reported occupational history
Greenland *et al.* (1994)[a]	US	Mort	Kidney	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	Kidney	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.* (2000a)	Germany	Inc	RCC	1991-1995	B	Median = 61-67	935	Population-based enrollment, hospitals in the study areas	4,298	Population-based enrollment, local residency registries	Interviews, self-reported job history, and JEM
Mattioli *et al.* (2002)	Italy	Inc	RCC	1987-1994	M	Median = 60-69	150	Hospital records	150	Hospital records	Self-reported occupational history
Brüning *et al.* (2003)	Germany	Inc	Kidney	1992-2000	B	Cases: 68 Controls: 66 (median)	134	Hospital records	401	Hospital records	Self-reported occupational history linked to JEM

Notes:
B = Both Males and Females; CaRP = Cancer of the Renal Pelvis; Inc = Incidence; JEM = Job-Exposure Matrix; M = Males; Mort = Mortality; RCC = Renal Cell Carcinoma, US = United States.
– = Not Reported.
(a) Restricted to white males (Greenland *et al.*, 1994).

Table H.4 Benzene and Kidney 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
McCredie and Stewart (1993)	Inc	RR	**RCC**					Age, sex, and method of interview
			Occupation/industry					
			Employed in other occupation/industry	–	–	Ref	–	
			Petroleum refining industry	15	11	1.01 (0.45-2.25)		
			Petrol station attendant	25	32	0.69 (0.40-1.21)		
			Specific occupational exposures					
			Not exposed to petrol/petroleum products	–	–	Ref	–	
			Petrol	53	48	1.23 (0.81-1.86)		
			Other petroleum products	64	39	**1.96 (1.28-2.99)**		
			CaRP					Age, sex, education, method of interview, smoking, and phenacetin containing analgesics
			Occupation/industry					
			Employed in other occupation/industry	–	–	Ref	–	
			Petroleum refining industry	8	11	2.60 (0.88-7.63)		
			Petrol station attendant	9	32	1.03 (0.46-2.30)		
			Specific occupational exposures					Age, sex, education, and method of interview
			Not exposed to petrol/petroleum products	–	–	Ref	–	
			Petrol	17	48	1.31 (0.70-2.46)		
			Other petroleum products	20	39	**2.16 (1.44-4.08)**		
Greenland *et al.* (1994)[a]	Mort	OR	No or indirect exposure[b]	–	–	Ref	–	Age and year of death
			Direct exposure	–	–	**4.29 (1.33-13.8)**		
Gérin *et al.* (1998)	Inc	OR	Unexposed	138	865	Ref	–	Age, family income, ethnicity, smoking, and respondent status (self or proxy)
			Low cumulative exposure	27	141	1.2 (0.7-1.9)		
			Medium/high cumulative exposure	12	60	1.3 (0.7-2.4)		
Pesch *et al.* (2000a)	Inc	OR	**Males**					Age, study center, and smoking

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p-trend	Covariate Adjustment
			Unexposed and low exposure[c]	–	–	Ref	–	
			Medium exposure	159	–	1.2 (1.0-1.5)		
			High exposure	156	–	1.2 (1.0-1.6)		
			Substantial exposure	52	–	1.4 (1.0-1.9)		
			Females					
			Unexposed and low exposure[c]	–	–	Ref	–	
			Medium exposure	60	–	1.4 (1.0-1.9)		
			High exposure	64	–	1.3 (1.0-1.8)		
			Substantial exposure	14	–	0.9 (0.5-1.7)		
Mattioli *et al.* (2002)	Inc	OR	**Professional Exposure to Petroleum Products**					Age, sex, birthplace, residence, BMI, smoking, coffee & alcohol consumption, and use of phenacetin and/or diuretics
			No	–	–	Ref	–	
			Yes	16	11	2.13 (0.58-7.88)		
Brüning *et al.* (2003)	Inc	OR	**Lifetime Exposure to Benzene Based on JEM[d]**					Age, sex, and smoking
			Not exposed	–	–	Ref	–	
			Low exposure	4	6	2.09 (0.56-7.78)		
			High exposure	5	6	2.19 (0.63-7.69)		

Notes:
CaRP = Cancer of the Renal Pelvis; CI = Confidence Interval; Inc = Incidence; JEM = Job Exposure Matrix; Mort = Mortality; OR = Odds Ratio; RCC = Rencal Cell Carcinoma; Ref = Reference.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Restricted to white males (Greenland *et al.*, 1994).
(b) Greenland *et al.* (1994) defined indirect exposure as "chemical in work area but worker does not perform tasks using it."
(c) Pesch *et al.* (2000a) and 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."
(d) Brüning *et al.* (2003) used the median of the exposure index as the cutoff between low and high categories.

Table H.5 Benzene and Kidney Cancer Meta-Analysis Results

Citation	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Metric	Risk Estimate (95% CI)
Seyyedsalehi *et al.* (2024)[a]	Meta-analysis	Inc & Mort	Kidney and urinary tract	29	Cohort & case-control	Random effects	Overall	RR	**1.20 (1.03-1.39)**
				4	Case-control[b]				**1.71 (1.12-2.43)**
				25	Cohort[b]				1.12 (0.95-1.32)
		Inc		16	Cohort & case-control				**1.17 (1.02-1.35)**
		Mort		17					1.18 (0.98-1.43)
		Inc & Mort		10			**Quality Score based on Newcastle-Ottawa Scale**		
							Low (<8)	RR	**1.31 (1.06-1.63)**
				19			High (≥8)		1.15 (0.97-1.36)
				2			**Dose Category**		
							Low	RR	1.00 (0.94–1.06)
				3			Medium		1.10 (0.89–1.35)
				4			High		**1.07 (1.02–1.13)**
				11			**Industry[b]**		
							Oil	RR	1.15 (0.94-1.39)
				5			Chemical		**1.54 (1.49-1.59)**
				6			Other		1.38 (0.97-1.96)
				4			Multiple		1.02 (0.99-1.05)
				3			Mixed[c]		0.91 (0.45-1.84)
				26			**Adjustment for Tobacco Smoking**		
							No	RR	**1.18 (1.01-1.39)**
				3			Yes		1.32 (0.90-1.92)

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; RR=Risk Ratio.
Bolded values indicate statistical significance.
(a) Stratified analyses by geographic region, year of publication, and sex were also provided. Statistically significant associations were observed for North American studies, studies published prior to the year 2000, and for women and both sexes. No heterogeneity between study groups was observed unless otherwise noted (Seyyedsalehi *et al.*, 2024).
(b) A significant p-value for heterogeneity in stratified analyses was reported (*i.e.*, for analyses by study design and industry) (Seyyedsalehi *et al.*, 2024).
(c) No definition is provided of "mixed" industries (Seyyedsalehi *et al.*, 2024).

Attachment I

Benzene Animal Carcinogenicity Studies

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Table I.1 Benzene and Kidney Cancer Chronic Oral Study Results

Study	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)	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
Huff *et al.* (1989); NTP (1986b)[a]	F3344/N Rat	104	104	50 M	0	0/50	1/50
					50	0/48	0/48
					100	0/48	0/48
					200	0/48	0/48
				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	1/50	0/50
					100	0/49	0/49
				50 F	0	0/50	0/50
					25	0/49	0/49
					50	0/50	1/50
					100	0/50	0/50

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

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

Study	Strain/Species	Exposure Duration (weeks)	Observation Period (weeks)	Treatment Groups (n Sex)	Concentration (ppm)	Cancer Outcome	
						Benign Tumors	Malignant Tumors
Snyder *et al.* (1978)	Sprague-Dawley Rat	Lifetime	Lifetime	27 M	0	NR	NR
				45 M	300	NR	NR
	AKR/J Mice			60 M	0	NR	NR
					300	NR	NR
Snyder *et al.* (1980)	AKR/J Mice	Lifetime	Lifetime	50 M	0	NR	NR
					100	NR	NR
	C57BL/6J Mice			40 M	0	NR	NR
					300	NR	NR
Maltoni *et al.* (1982, 1985, 1983, 1989)	Sprague-Dawley Rat	104	Until spontaneous death	158 M	0	0/158	0/158
				75 M	200-300	0/75	0/75
				149 F	0	0/149	0/149
				60 F	0	0/60	0/60
				54 F	200-300	0/54	0/54
				65 F	200-300	0/65	1/65
Snyder *et al.* (1984)	Sprague-Dawley Rat	Lifetime	Lifetime	40 M	0	NR	NR
					100	NR	NR
Snyder *et al.* (1988)	C57BL/6 Mice	Lifetime	Lifetime	60 M	0	NR	NR
					300	NR	NR
	CD-1 Mice			60 M	0	NR	NR
					300	NR	NR

Notes:
F = Female; M = Male; NR = Kidney was analyzed, but kidney tumor findings were not reported; ppm = Parts Per Million.

Table I.3 Benzene and Kidney 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. Snyder *et al.* (1978, 1980, 1984, 1988) and the oral studies by Maltoni *et al.* (1982, 1985, 1983, 1989) stated that they examined the kidney but did not report any kidney tumor data.
Allocation	All studies indicated that animals were randomly allocated to dose groups.
Bias	There was no indication of bias due to co-exposures, vehicle, diet, palatability, husbandry, or health status.
Sample	Only Huff *et al.* (1989)/NTP (1986b), Snyder *et al.* (1988), and the Maltoni *et al.* (1982, 1985, 1983, 1989) inhalation bioassays 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)/NTP (1986b) identified the benzene source and confirmed purity. Snyder *et al.* (1984, 1988) identified the benzene source but did not confirm 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, 1986b), but two were 52 weeks (Maltoni *et al.*, 19791983, 1985, 1988b, 1989) and one was 78 weeks (Maltoni *et al.*, 1983, 1985, 1988b, 1989). In seven bioassays, rodents were treated and observed throughout their lifespan (Snyder *et al.*, 1978, 1980, 1984, 1988). A single dose was tested in four chronic oral bioassays (Maltoni *et al.*, 1983, 1985, 1988b, 1989) and seven inhalation bioassays (Snyder *et al.*, 1978, 1980, 1984, 1988). Only three oral bioassays tested more than one dose (Maltoni *et al.*, 1979; 1983, 1985, 1988b, 1989; Huff *et al.*, 1989/NTP, 1986b). Snyder *et al.* (1980, 1978) reported that treatment with 300 ppm benzene resulted in high mortality of animals
Outcome Assessment	Maltoni *et al.* (1983, 1985, 1988b, 1989) examined animals after spontaneous death rather than after sacrifice. Also, 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." Snyder *et al.* (1978, 1980, 1984, 1988) also observed animals over their entire lifespan. Huff *et al.* (1989); NTP (1986b) observed mice for 104 weeks.

Notes:
ppm = Parts Per Million; RI = Ramazzini Institute.

Table I.4 Benzene and Kidney Cancer Chronic Toxicity Study Quality Assessment

Study	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
Maltoni *et al.* (1979; 1983, 1985, 1988b, 1989)	**Allocation** **Bias**	**Reporting:** No kidney tumor data **Sample:** Sample sizes too small **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Exposure duration too short in some bioassays **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data
Huff *et al.* (1989); NTP (1986b)	**Reporting** **Allocation** **Bias** **Sample** **Chemical Administration and Characterization** **Exposure Timing, Dose and Duration** **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			
Snyder *et al.* (1978)	**Allocation** **Bias**	**Reporting:** No kidney tumor data **Sample:** Small sample size (controls) **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Only one concentration tested; lifetime exposure **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data
Snyder *et al.* (1980)	**Allocation** **Bias**	**Reporting:** No kidney tumor data **Sample:** Small sample size (C57BL/6J Mice) **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data

Study	Strengths	Weaknesses	Human Relevance
Maltoni *et al.* (1982, 1985, 1983)	**Reporting** **Allocation** **Bias** **Sample** **Exposure Conditions**	**Chemical Administration and Characterization:** Did not identify benzene source or report purity **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Snyder *et al.* (1984)	**Allocation** **Bias**	**Reporting:** No kidney tumor data **Sample:** Small sample size **Chemical Administration and Characterization:** Did not conduct independent verification of chemical purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data
Snyder *et al.* (1988)	**Allocation** **Bias** **Sample**	**Reporting:** No kidney tumor data **Chemical Administration and Characterization:** Did not conduct independent verification of chemical purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data

Attachment J

Vinyl Chloride Epidemiology Studies

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

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

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

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Years)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	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	Kidney and other urinary organs	SSA, NDI, company mortality register, benefit records, and death certificates	1974-1983
Bove *et al.* (2014a)	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	Kidney	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[a] CP: 34-60[a]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Kidney	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	Work assignment at chemical manufacturing plant (*i.e.*, assignment to a department, job, or location where vinyl chloride exposures could have occurred)	Mort	Kidney	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	Kidney	NDI, death certificates	1942-2013

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Years)	N Total (Analytical)	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
ATSDR (2018b)[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	Kidney	Self-report confirmed by medical records or death certificates	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; VC = Vinyl Chloride; 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.*, 2014a,b).
(b) Mean age at hire (Mundt *et al.*, 2017).
(c) 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, 2018b).
(d) Median age at survey or death (ATSDR, 2018b).

Table J.2 Vinyl Chloride and Kidney 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
Teta *et al.* (1990)	US white males	Mort	SMR	Hourly male employees in the Chemicals and Plastics business group	8	4.6	1.74 (0.75-3.43)	–	Age, sex, and calendar yr
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines and Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-months) with 10-yr lag					
				No/low (0-205)[b]	22	–	0.91 (0.46-1.78)	–	
				Medium/high (>205-2,800)[b]	20		1.55 (0.94-2.57)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-months[c]			Low (>1-205)	10		1.66 (0.68-4.04)		
				Medium (>205-500)	10		1.61 (0.65-3.98)		
				High (>500-2,800)	10		1.51 (0.61-3.74)		
Bove *et al.* (2014b)	CL civilian employees with exposure <median	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Maximum cumulative exposure level with 10-yr lag[c]					
				≥Median	7	0	∞	–	
Carreón *et al.* (2014)	US general population	Mort	SMR	All Workers	2	–	0.64 (0.08-2.33)	–	Age, sex, race, and calendar yr
				Duration of Employment (Days)					
				<90	1	–	1.84 (0.05-10.24)	–	
				≥90	1		0.39 (0.01-2.18)		
Mundt *et al.* (2017)	NIOSH state-specific groups for white men	Mort	SMR	Overall	52	44.6	1.16 (0.87-1.53)	–	Age, calendar year and plant type (VC *vs.* PVC)
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**Cumulative Exposure Level[d,e]**					Age and sex
				Low	82	–	0.90 (0.56-1.45)	–	
				Medium	86		1.33 (0.84-2.13)		
				High	24		1.42 (0.78-2.58)		
	CL Marines & Navy personnel with low exposure[f]			Medium	86		**1.45 (1.05-2.00)**		
				High	24		1.55 (0.95-2.54)		

Notes (continued on next page):

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

– = 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*., 2014a). I report the values consistent with the text definition.

(c) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were positive but non-significant (Bove *et al*., 2014a,b).

(d) 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).

(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 and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).

(f) ATSDR (2018b) reported a monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

Attachment K

Vinyl Chloride Animal Carcinogenicity Studies

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

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

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

Reference	Strain/ Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-day)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Sprague-Dawley rats	52-59	Until spontaneous death	40 M	0	0/40	0/40
					3.33	0/40	0/40
					16.65	0/40	2/40
					50	0/40	1/40
				40 F	0	0/40	0/40
					3.33	0/40	0/40
					16.65	0/40	1/40
					50	0/40	1/40
	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	1/75
					0.03	0/75	0/75
					0.3	0/73	0/73
					1	0/75	1/75
Feron *et al.* (1981)[b]	Wistar rats	135	M: 135 weeks F: 144 weeks	80 M	0	0/80	1/80
				60 M	1.7	0/60	0/60
					5.0	0/60	0/60
				80 M	14.1	0/80	1/80
					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	1/80
					300	0/80	0/80

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

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

Citation	Strain/ Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney 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	0/29	0/29
					50	0/30	0/30
					250	1/29	1/29
					500	0/30	2/30
					2,500	1/30	5/30
					6,000	0/29	4/29
					10,000	0/30	3/30
				30 F	0	0/29	0/29
					50	0/30	1/30
					250	0/30	4/30
					500	0/30	4/30
					2,500	0/30	1/30
					6,000	0/30	1/30
					10,000	0/30	2/30
	Sprague-Dawley rats	52 weeks		85 M	0	0/85	0/85
				60 M	100	1/60	8/60
					150	0/59	8/59
					200	1/60	5/60
				100 F	0	0/100	0/100
				60 F	100	0/60	2/60
					150	0/60	3/60
					200	0/60	2/60
	Sprague-Dawley rats	52 weeks		30 M	30,000	0/30	0/30
				30 F		0/30	0/30
	Wistar rats	52 weeks		40 M	0	0/38	0/38
				30 M	50	0/28	1/28
					250	1/27	0/27
					500	0/28	2/28

Citation	Strain/ Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
					2,500	0/25	0/25
					6,000	1/26	2/26
					10,000	0/27	1/27
	Sprague-Dawley rats	52 weeks		50 M	0	0/48	0/48
				150 M	50	0/144	0/144
				50 F	0	0/50	0/50
				150 F	50	0/150	2/150
	Sprague-Dawley rats	52 weeks		60 M	0	0/60	0/60
					1	0/58	0/58
					5	1/59	1/59
					10	0/59	0/59
					25	0/60	1/60
				60 F	0	0/60	1/60
					1	0/60	1/60
					5	0/60	1/60
					10	0/60	0/60
					25	0/60	1/60
	Wistar rats	52 weeks		120-130 M	0	0/94	1/94
					1	2/99	2/99
Holmberg *et al.* (1976)	NMRI mice	52 weeks	Until moribund or spontaneously death	12 M	0	NR	NR
					50	NR	NR
				12 F	0	NR	NR
					50	NR	NR
Lee *et al.* (1978)	CD-1 mice	52 weeks	52 weeks	36 M	0	NR	NR
					50	NR	NR
					250	NR	NR
					1,000	NR	NR
				36 F	0	NR	NR
					50	NR	NR
					250	NR	NR

Citation	Strain/ Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
					1,000	NR	NR
	CD rats	52 weeks		36 M	0	NR	NR
					50	NR	NR
					250	NR	NR
					1,000	NR	NR
				36 F	0	NR	NR
					50	NR	NR
					250	NR	NR
					1,000	NR	NR
Feron and Kroes (1979)[a]	Wistar rats	52 weeks	52 weeks	10 M	0	NR	NR
					5,000	NR	NR
				10 F	0	NR	NR
					5,000	NR	NR
Drew *et al.* (1983)[b]	F344 rats	0 months	Until moribund or spontaneously death	112 F	0	NR	NR
		0-12 months		56 F	100	NR	NR
		0-18 months		55 F		NR	NR
		0-24 months		55 F		NR	NR
		6-18 months		54 F		NR	NR
		12-24 months		49 F		NR	NR
	Golden Syrian hamsters	0 months		143 F	0	NR	NR
		0-12 months		52 F	200	NR	NR
		0-18 months		103 F		NR	NR
		6-18 months		44 F		NR	NR
		12-24 months		43 F		NR	NR
	CD-1 Swiss mice	0 months		69 F	0	NR	NR
		0-12 months		90 F	50	NR	NR
		0-18 months		—		NR	NR
		6-18 months		48 F		NR	NR
		12-24 months		48 F		NR	NR
	B6C3F1 mice	0 months		69 F	0	NR	NR
		0-12 months		90 F	50	NR	NR
		0-18 months		—		NR	NR
Bi *et al.* (1985)	Wistar rats	52 weeks	18 months	75 M	0	NR	NR

Citation	Strain/ Species	Exposure Duration (Weeks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Kidney Cancer Outcome	
						Benign Tumors	Malignant Tumors
					10	NR	NR
					100	NR	NR
					3,000	NR	NR
Maltoni and Cotti (1988)[c]	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 = Kidney was analyzed, but kidney tumor findings were not reported; ppm = Parts Per Million.
— = Not examined.
(a) Ante-mortem findings of focal proliferation of atypical tubular epithelium in one male and metastasis of a mesenchymal-type lung tumor to the kidneys in one female, both in the 5,000 ppm group (Feron and Kroes, 1979).
(b) Some dose groups were exposed for 6, 12, 18, or 24 months (rats and hamsters only). Other groups were held for 6 months or 12 months (rats and hamsters only) and then exposed for 6 or 12 months. This resulted in 10 unique exposure groups for rats and hamsters, and 8 exposure groups for mice. None of the scheduled 0- to 18-month-exposed mice survived for more than 1 year. The starting number of animals presented in Table K.2 is based on the highest incident denominator because original "n" values were not reported (Drew *et al.*, 1983).
(c) 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 Kidney Cancer Chronic Intraperitoneal Injection Study Results

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

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

Table K.4 Vinyl Chloride and Kidney 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. However, the majority of bioassays that stated they examined the kidney did not report any kidney tumor findings. The only exceptions were Maltoni and Lefemine (1975), Maltoni *et al.* (1981, 1984) (for oral and inhalation exposure), and Feron *et al.* (1981).
Allocation	With the exception of Feron *et al.* (1981), Drew *et al.* (1983), and Bi *et al.* (1985), studies 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; exceptions were Holmberg *et al.* (1976), Lee *et al.* (1978), and Feron and Kroes (1979). All animals were accounted for in the studies by Holmberg *et al.* (1976), Drew *et al.* (1983), and Maltoni and Cotti (1988).
Chemical Administration and Characterization	Only four bioassays (Feron *et al.*, 1981; Lee *et al.*, 1978; Bi *et al.*, 1985; Maltoni and Cotti, 1988) provided adequate information on chemical source, purity, or composition; independently verified chemical purity; and took steps to ensure reported exposure levels were accurate. The remaining bioassays did not.
Exposure Conditions	The duration of exposure was not adequate in any study. Fifteen chronic bioassays exposed animals for 52 weeks (Maltoni and Lefemine, 1975; Maltoni *et al.*, 1981, 1984; Holmberg *et al.*, 1976; Lee *et al.*, 1978; Feron and Kroes, 1979; Bi *et al.*, 1985), and one chronic bioassay exposed animals for 76 weeks (Maltoni and Cotti, 1988). Drew *et al.* (1983) exposed animals for various amounts of time, ranging from 12 to 18 months (CD-1 and B6C3F1 mice) or 12 to 24 months (F344 rats and golden Syrian hamsters). Feron *et al.* (1981) exposed animals for 135-144 weeks, based on the point at which 75% of the control rats were dead. Seven chronic inhalation bioassays tested only a single concentration of vinyl chloride (Holmberg *et al.*, 1976; Feron and Kroes, 1979; Drew *et al.*, 1983; Maltoni and Cotti, 1988).
Outcome Assessment	Bi *et al.* (1985) used a reliable, valid, sensitive, and specific outcome assessment method and an appropriate observation period. The studies by Feron and Kroes (1979) and Lee *et al.* (1978) only observed rats and mice for 52 weeks, which is too short for evaluating carcinogenicity. All remaining 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 Kidney 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 duration 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 **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)	**Reporting** **Bias**	**Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for **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
Holmberg *et al.* (1976)	**Bias**	**Reporting:** No kidney 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 kidney tumor data
Lee *et al.* (1978)	**Bias** **Chemical Administration and Characterization**	**Reporting:** No kidney tumor data **Allocation:** Did not specify whether random **Sample:** Small sample size and not all animals were accounted for **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too short	**None:** No kidney tumor data
Feron and Kroes (1979)	**Bias**	**Reporting:** No kidney tumor data **Allocation:** Did not specify whether random **Sample:** Small sample size and not all animals were accounted for **Chemical Administration and Characterization:** Did not identify vinyl chloride source, confirm purity, or ensure reported exposure levels were accurate **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment:** Observation period too short	**None:** No kidney tumor data
Drew *et al.* (1983)	**Allocation** **Bias** **Sample**	**Reporting:** No kidney tumor data **Chemical Administration and Characterization:** Did not confirm purity of vinyl chloride **Exposure Conditions:** Exposure duration too short and only one dose tested per species **Outcome Assessment:** Observation period too long	**None:** No kidney tumor data

Citation	Strengths	Weaknesses	Human Relevance
Bi *et al.* (1985)	**Allocation** **Chemical Administration and Characterization** **Bias** **Outcome Assessment**	**Reporting:** No kidney tumor data **Sample:** Not all animals are accounted for **Exposure Conditions:** Exposure duration too short	**None:** No kidney tumor data
Maltoni and Cotti (1988)	**Chemical Administration and Characterization** **Bias** **Sample**	**Reporting:** No kidney 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 kidney tumor data
Chronic — Intraperitoneal Injection			
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	**Bias**	**Reporting:** No kidney tumor data **Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for **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 kidney tumor data

Attachment L

Curriculum Vitae

Julie E. Goodman, Ph.D., DABT, FACE, ATS
Principal
Julie.Goodman@gradientcorp.com

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*

Rhomberg, LR; Goodman, JE; Ryman, J. 2025, Forthcoming. "Is the Science Underlying Recent Alternatives for Harmonizing Quantitative Risk Approaches Robust Enough to Replace Toxicity Thresholds in Non-Cancer Risk Assessment? " *J. Toxicol. Reg. Pol.*

Bus, JS; Su, S; Li, W; Goodman, JE. 2024. "Styrene Lung Cancer Risk Assessment: An Alternative Evaluation of Human Lung Cancer Risk Assuming Mouse Lung Tumors are Potentially Human Relevant and Operating by a Threshold-based Non-genotoxic Mode of Action." *J. Toxicol. Environ. Health B Crit. Rev.* 27(7):264-286. doi: 10.1080/10937404.2024.2380449.

Prueitt, RL; Goodman, JE. 2024. "Real-world Bisphenol A Exposure Not Linked to Microbiota Dynamics in Childhood Obesity." *mSystems.* 9(7):e0055624. doi: 10.1128/msystems.00714-24.

Boon, DN; Goodman, JE; Colonna, KJ; Espira, LM; Prueitt, RL. 2024. "A Systematic Review of the Epidemiology Evidence on Talc and Cancer." *Crit. Rev. Toxicol.* 54(6):394-417. doi: 10.1080/10408444.2024.2351081.

Prueitt, RL; Drury, NL; Shore, RA; Boon, DN; Goodman, JE. 2024. "Talc and Human Cancer: A Systematic Review of the Experimental/Animal and Mechanistic Evidence." *Crit. Rev. Toxicol.* 54(6):359-393. doi: 10.1080/10408444.2024.2349668.

Goodman, JE; Espira, LM; Zu, K; Boon, D. 2024. "Quantitative Recall Bias Analysis of the Talc and Ovarian Cancer Association." *Glob. Epidemiol.* 7:100140. doi: 10.1016/j.gloepi.2024.100140.

Li, W; Goodman, JE; Long, CM. 2024. "Population Attributable Fraction of Gas Cooking and Childhood Asthma: What Was Missed?" *Glob. Epidemiol.* 7:100141. doi: 10.1016/j.gloepi.2024.100141.

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Tao, G; Zu, K; Long, CM; Goodman, JE; Valberg, PA. 2015. "Forest-fire Fine Particulate Matter and Daily Mortality in Greater Boston and New York City." *Toxicologist* 144(1):163. Abstract 763. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Zu, K; Tao, G; Kerper, LE; Rhomberg, LR; Goodman, JE. 2015. "Evaluation of US EPA's Noncancer Risk Assessment of Libby Amphibole Asbestos." *Toxicologist* 144(1):164. Abstract 768. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Sax, SN; Pizzurro, DM; Zu, K; Lynch, HN; Prueitt, RL; Goodman, JE. 2015. "Ozone Exposure and Systemic Biomarkers: Evaluation of Evidence of Adverse Cardiovascular Health Impacts." *Toxicologist* 144(1):166-167. Abstract 778. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Prueitt, RL; Lynch, HN; Tabony, JA; Beck, NB; Goodman, JE; Rhomberg, LR 2015. "Evaluation of Study Quality Criteria Frameworks." *Toxicologist* 144(1):400. Abstract 1865. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Kerper, LE; Lynch, HN; Zu, K; Tao, G; Utell, M; Goodman, JE. 2015. "A Systematic Review of Asbestos-induced Pleural Plaques and Lung Function." *Toxicologist* 144(1):401. Abstract 1869. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Seeley, MR; Thakali, S; Goodman, JE. 2015. "Birth Defect Rates in High and Low Atrazine-use States." *Toxicologist* 144(1):462. Abstract 2151. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Loftus, CT; Goodman, JE; Zu, K. 2015. "2,4-dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma, Gastric Cancer, and Prostate Cancer: Meta-analyses of the Published Literature." *Toxicologist* 144(1 (Supplement)):192. Abstract 2831. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Goodman, JE; Lynch, HN; Prueitt, RL; Beck, NB; Tabony, JA; Rhomberg, LR. 2014. "Evaluation of Study Quality Criteria Frameworks." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Sax, SN; Pizzurro, DM; Zu, K; Lynch, HN; Prueitt, RL; Goodman JE. 2014. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Biomarkers." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Lange, SS; Rhomberg, LR; Dourson, ML, Tao G, Goodman JE, Honeycutt M. 2014. "How Dose Response Curves Derived from Clinical Ozone Exposures can Inform Public Policy." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Kerper, LE; Lynch, HN; Mohr, LC; Goodman, JE. 2014. "Do Asbestos-induced Pleural Plaques Cause Lung Function Deficits?" *Toxicologist* 138(1):475. Abstract 1811. Presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ, March 23-27.

Prueitt, RL; Sax, SN; Lynch, HN; Lemay, JC; King, JM; Goodman, JE. 2014. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects." *Toxicologist* 138(1):475. Abstract 1810. Presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ, March 23-27.

Lemay, JC; Prueitt, RL; Hixon, ML; Goodman, JE. 2013. "Distinguishing between Risks and Hazards: A Case Study of Bisphenol A." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 810. 13p.

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.

Goodman, JE, Prueitt RL, Rhomberg, LR. 2013. "Hypothesis-based Weight-of-evidence Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." Presented at the Conference on Isocyanates and Health: Past, Present and Future, April 3-4.

Seeley, MR; Goodman, JE. 2013. "Is There a Subset of Susceptible Individuals in Controlled Air Pollution Studies?" *Toxicologist* 132(1):414. Abstract No. 1945. Presented at the Society of Toxicology (SOT) 52nd Annual Meeting, San Antonio, TX, March 10-14.

Prueitt, RL; Goodman, JE; Rhomberg, LR. 2013. "Hypothesis-based Weight-of-evidence Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." *Toxicologist* 132(1):415. Abstract No. 1951. Presented at the Society of Toxicology (SOT) 52nd Annual Meeting, San Antonio, TX, March 10-14.

Rhomberg, LR; Goodman, JE; Bailey, EA; Prueitt, RL. 2012. "Weight-of-evidence Frameworks, Systems, and Tools: A Survey of Existing Approaches and Notes on Best Practices." Presented at the "Putting it All Together: Recent Developments in Risk Assessment Approaches" Symposium, Society for Risk Analysis Annual Meeting, San Francisco, CA, December 11. 24p.

Sax, SN; Lau, JH; Goodman, JE. 2012. "Evaluation of the BenMAP Model for Estimating Mortality Impacts of Lower Ozone Concentrations." Presented at the 22nd Annual Conference of the International Society of Exposure Science, Seattle, WA, October 28-November 1.

Bailey, LA; Goodman, JE; Beck, BD. 2012. "Revised Reference Concentration for Manganese Oxide Based on Recent Epidemiology and Pharmacokinetic Studies." *Toxicologist* 126(1):213. Abstract No. 995. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Peterson, MK; Goodman, JE. 2012. "Infant Risk and Exposure Assessment of Bisphenol A in Polycarbonate and 'BPA-free' Plastic Bottles." *Toxicologist* 126(1):319. Abstract No. 1478. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Prueitt, RL; Goodman, JE; Bailey, LA; Rhomberg, LR. 2012. "Hypothesis-based Weight-of-evidence Evaluation of the Neurodevelopmental Effects of Chlorpyrifos." *Toxicologist* 126(1):309. Abstract No. 1430. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Seeley, MR; Goodman, JE. 2012. "Is Sulfur Dioxide a Reproductive and Developmental Toxicant?" *Toxicologist* 126(1):24. Abstract No. 119. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

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.

Prueitt, RL; Goodman, JE. 2011. "Evaluation of Adverse Effects on Human Lung Function Caused by Ozone." *Toxicologist* 120(Suppl. 2):491. Abstract No. 2286. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Peterson, MK; Bailey, LA; Dodge, DG; Goodman, JE; Valberg, PA. 2011. "A Weight-of-evidence Evaluation of Asbestos Exposure and Mesothelioma Risk among Electricians." *Toxicologist* 120(Suppl. 2):414. Abstract No. 1935. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Goodman, JE; Mayfield, DB; Bailey, LA; Rhomberg, LR. 2011. "Weight-of-evidence Evaluation of Formaldehyde Exposure and Leukemia Risk." *Toxicologist* 120(Suppl. 2):416. Abstract No. 1944. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Mattuck, RL; Seeley, MR; Reid, KR; Goodman, JE. 2011. "Human Health Risks from Exposure to 1,4-butanediol in Craft Kit Beads." *Toxicologist* 190(Suppl. 2):332. Abstract No. 1545. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Dodge, DG; Pollock, MC; Sax, SN; Petito Boyce, C; Goodman, JE. 2011. "Risk Characterization of the Brominated Flame Retardant Decabromodiphenyl Ethane in Indoor Dust." *Toxicologist* 120(Suppl. 2):271. Abstract No. 1268. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Peterson, MK; Bailey, LA; Dodge, DG; Goodman, JE; Valberg, PA. 2010. "Risk Assessment of Mesothelioma Among Electricians." Presented at the Society for Risk Analysis Annual Meeting, Salt Lake City, UT, December 5-8.

Haber, LT; Prueitt, RL; Goodman, JE; Thakali, S; Patterson, J. 2010. "Report of a Workshop: An Evaluation of Hypotheses for Determining the Carcinogenic Potential of Nickel-containing Substances." Presented at the Society for Risk Analysis Annual Meeting, Salt Lake City, Utah, December 5-8. 1p.

Goodman, JE; Kerper, LE; Petito Boyce, C; Prueitt, RL; Rhomberg, LR. 2010. "Weight of Evidence Exposures Analysis of Exposures to Dioxins and Dioxin-like Compounds and Associations with Thyroid Hormone Levels during Early Development." Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT. 1p.

Prueitt, RL; Goodman, JE; Thakali, S. 2010. "An Evaluation of Hypotheses for Determining the Carcinogenic Potential of Nickel-containing Substances." Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT. 1p.

Dodge, DG; Goodman, JE; Beck, BD. 2010. "Weight-of-evidence Analysis of Hydroquinone and Leukemia." *Toxicologist* 114(1):111-112. Abstract No. 514. Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT, March 7-11.

Thakali, S; Chandalia, JK; Seeley, M; Goodman, JE. 2010. "Meta-analysis of Nitrogen Dioxide Effects on Airway Hyper-responsiveness in Asthmatics: Effects of the Types of Airway Challenge, Exposure Methods, and Activites During Exposure." *Toxicologist* 114(1):401. Abstract No. 1886. Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT, March 7-11.

Goodman, JE; Chandalia, JK; Thakali, S; Seeley, M. 2009. "Meta-analysis of Controlled Nitrogen Dioxide Exposure Studies Assessing Airway Hyper-responsiveness in Asthmatics." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 6-9.

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.

Prueitt, RL; Goodman, JE; Dodge, DG; Thakali, S. 2009. "A Weight-of-evidence Evaluation of the Carcinogenicity of Soluble Nickel." *Toxicologist* 108(1):328. Abstract No. 1582. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Goodman, JE; Rhomberg, LR. 2009. "A Weight-of-evidence Approach to Evaluating Epidemiological Data on Styrene Cancer Hazards." *Toxicologist* 108(1):248. Abstract No. 1190. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Beyer, LA; Beck, BD; Goodman, JE. 2009. "Background Rates of Lymphomas/Leukemias and Leydig Cell Tumors in Sprague Dawley Rats." *Toxicologist* 108(1):421. Abstract No. 2028. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Goodman, JE; Bailey, LA; Beck, BD. 2008. "Recent Occupational Studies of Manganese and their Bearing on the Reference Concentration (RfC)." Presented at the Annual Meeting of the American College of Epidemiology, Tucson, AZ, September 14-16.

Aylward, LL; Goodman, JE; Charnley, G; Rhomberg, LR. 2008. "A Margin of Exposure Approach to Assessment of Non-cancer Risks of Dioxins Based on Human Exposure and Response Data." Presented at the 28th International Symposium on Halogenated Persistent Organic Pollutants, Birmingham, England, August 17-22.

Goodman, JE; Bailey, LA; Beck, BD. 2008. "Recent Studies of the Health Effects of Manganese and the Implications for the Reference Concentration (RfC)." *Toxicologist* 102. Abstract No. 1787. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Dodge, DG; Haber, LT; Kopras, E; Goodman, JE; Pagan, I; Gift, JS; Rhomberg, LR. 2008 "Case Studies for the Development of a Pathophysiological Progression Model." *Toxicologist* 102(1):245. Abstract No. 1189. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Beyer, LA; Slayton, TM; Goodman, JE; Greenberg, GI; Hudson, TC; Sax, SN; Beck, BD. 2008 "Evaluation of Key Information Informing the Basis of EPA's New Recommended Ozone Standard." *Toxicologist* 102. Abstract No. 1462. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Pagan, I; Haber, LT; Rhomberg, LR; Goodman, JE; Dodge, DG; Foureman, GL. 2007. "Development of a Pathophysiological Progression Model for Selected Endpoints." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

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.

Mechanic, LE; Luke, BT; Goodman, JE; Chanock, SJ; Harris, CC. 2007. "Polymorphism Interaction Analysis (PIA): A Method for Investigating Complex Gene-gene Interactions." Presented at Approaches to Complex Pathways in Molecular Epidemiology, Santa Ana Pueblo, NM, May 30-June 2.

Goodman, JE; Gaylor, D; Beyer, LA; Rhomberg, LR; Beck, BD. 2007. "MTBE is Not Associated with a Statistically Significant Increase in Leydig Cell Tumors in Sprague-Dawley Rats." *Toxicologist* 96(1):339. Abstract No. 1637. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

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.

Schoen, A; Eldan, M; Goodman, JE; Beck, BD. 2006. "DMA_V-induced Bladder Tumors: Unique Rat Susceptibility." *Toxicologist* 90(1):448. Abstract No. 2186. Presented at the Society of Toxicology (SOT) 45th Annual Meeting, San Diego, CA, March 5-9.

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.

Goodman, JE; He, P; Yager, JD. 2002. "COMT Polymorphism and Catechol Estrogen Methylation in Breast Epithelial Cell Lines." *Proc. Am. Assoc. Cancer Res.* 45.

Goodman, JE; He, P; Yager, JD. 2001. "Kinetics of High and Low Activity Human Catechol-O-methyltransferase Activity for Catechol Estrogen Methylation." *Proc. Am. Assoc. Cancer Res.* 42.

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