Exhibit 134

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene and Parkinson's Disease

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Abbreviations

1,1,1-TCA	1,1,1-Trichloroacetic Acid
A30P	Mutant Human α-Synuclein
AIC	Akaike's Information Criterion
ALP-SENF	Alpha Pinene-Loaded Self-Emulsifying Nano-Formulation
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
bw	Body Weight
CCl_4	Carbon Tetrachloride
CI	Confidence Interval
CIR	Confidence Interval Ratio
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DCE	Dichloroethylene
DLB	Dementia with Lewy Bodies
DMDC	Defense Manpower Data Center
FINJEM	Finnish Job Exposure Matrix
HR	Hazard Ratio
i.p.	Intraperitoneal
IOM	Institute of Medicine
IRIS	Integrated Risk Information System
IRR	Incidence Rate Ratio
IRS	Internal Revenue Service
JEM	Job Exposure Matrix
LRRK2	Leucine-Rich Repeat Kinase 2
mmHg	Millimeters of Mercury
MoA	Mode of Action
MCLG	Maximum Contaminant Level Goal
MCL	Maximum Contaminant Level
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTD	Maximum Tolerated Dose
NAS	National Academy of Sciences
NASEM	National Academies of Sciences, Engineering, and Medicine
NDI	National Death Index
NINDS	National Institute of Neurological Disorders and Stroke
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OMB	Office of Management and Budget
OR	Odds Ratio
ORES	Office of Research, Evaluation and Statistics

PAF	Population Attributable Fraction
PBA	Probabilistic Bias Analysis
PBPK	Physiologically Based Pharmacokinetic
PCE	Perchloroethylene
PD	Parkinson's Disease
PMR	Proportionate Mortality Ratio
ppb	Parts per Billion
ppm	Parts per Million
ppt	Parts per Trillion
PVC	Polyvinyl Chloride
RfD	Reference Dose
RR	Relative Risk
SciRAP	Science in Risk Assessment and Policy
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SNpc	*Substantia Nigra Pars Compacta*
$Sod1^{-/-}$	Superoxide Dismutase 1
SSA	Social Security Administration
TaClo	1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline
TCA	Trichloroacetic Acid
TCE	Trichloroethylene
TCOH	Trichloroethanol
TVOC	Total Volatile Organic Compounds
US	United States
US EPA	United States Environmental Protection Agency
USMC	United States Marine Corps
VA	Veterans Affairs
VHA	Veterans Health Administration
VOC	Volatile Organic Compound

1 Overview

This report was prepared at the request of counsel for Defendants *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 Parkinson's disease (PD) 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 occupational or environmental exposure to these chemicals and PD. My opinions are based on a review of the published literature, including a substantial number of scientific and regulatory documents, as well as my training and experience in epidemiology, toxicology, and risk assessment.

Below I provide an overview of my opinions regarding TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE exposure and PD. My credentials are discussed in Section 2. After describing scientific principles and my methodology in Section 3, I provide an overview of PD 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. Section 6 describes the epidemiology, toxicology, and mode-of-action (MoA) evidence regarding TCE and PD, 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 comment on Plaintiffs' experts' opinions in Section 11, and my overall conclusions on all five chemicals and PD are presented in Section 12. Attachment A describes my literature search methods and Attachments B through H include tables with information on epidemiology and toxicity study quality, characteristics, and results. My *curriculum vitae* and testimony experience are provided in Attachments I and J, respectively.

1.1 Camp Lejeune

I identified four cohort studies that evaluated PD risks in United States (US) Marines and Navy personnel or civilian employees at Camp Lejeune. 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 PD. Most risk estimates were statistically null, and the few statistically significant risk estimates were not reported across other analyses of the Camp Lejeune population. These studies all had several methodological limitations, including a high likelihood of exposure misclassification, a lack of adjustment for relevant covariates like alcohol use, and a potential for selection bias. NRC (2009) concluded "limitations in population size, data availability, and data quality cannot be overcome." There are no toxicity or mechanic studies of Camp Lejeune drinking water, but toxicity and mechanistic studies, in general, do not provide evidence that exposures to TCE, PCE, or vinyl chloride can cause PD.

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

1.2 TCE

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

Few epidemiology studies have evaluated associations between TCE exposure and PD. These studies have mixed results, and several methodological limitations, including that they lack direct measurements of individual-level TCE exposures. As such, these studies do not provide evidence for an association between TCE exposure and PD.

There is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD. While subchronic- and subacute-duration experimental animal studies have reported some PD-associated pathological or behavioral effects in rats and mice exposed to very high concentrations of TCE, the exposure conditions are not relevant to human exposures, and the magnitudes of effects (specifically on dopamine levels and dopaminergic neuron loss in the substantia nigra pars compacta [SNpc]) were below those necessary to produce clinical signs of PD in humans. Also, some behavioral effects were not consistent within or across studies. Finally, there is no confirmed mechanism by which TCE could affect the dopaminergic system in laboratory animals or humans.

The Agency for Toxic Substances and Disease Registry (ATSDR) "Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (2017a), which was written by one person over a period of 6 weeks, concluded that "epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above," but "there is equipoise and above evidence for causation for TCE and Parkinson disease" based on "strong supporting mechanistic evidence." This conclusion is inconsistent with all other agency reviews, including the ATSDR Toxicological Profile, none of which concluded that TCE is a known cause of PD.

My opinion is that, as a whole, the currently available evidence does not support a causal association between TCE exposure and PD.

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.

Few epidemiology studies have evaluated associations between PCE exposure and PD. Collectively, these studies do not provide evidence for an association between PCE exposure and PD. Most analyses do not provide evidence of associations, and these studies have several methodological limitations, including that they lack direct measurements of individual-level PCE exposures. PD has not been evaluated in PCE animal studies. No scientific or regulatory agency has concluded that PCE is a known cause of PD.

My opinion is that, as a whole, the currently available evidence does not support a causal association between PCE exposure and PD.

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 applied 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.

No epidemiology or animal studies have evaluated benzene exposure alone and PD. No scientific or regulatory agency has addressed whether benzene is a known cause of PD. There is no evidence that benzene exposure can cause PD. My opinion is that, as a whole, the currently available evidence does not support a causal association between benzene exposure and PD.

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.

No epidemiology or animal studies have evaluated vinyl chloride exposure alone and PD. No scientific or regulatory agency has addressed whether vinyl chloride is a known cause of PD. There is no evidence that vinyl chloride exposure can cause PD. My opinion is that, as a whole, the currently available evidence does not support a causal association between vinyl chloride exposure and PD.

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 exposure and PD.

1.7 Agency Reviews

Chemical toxicity is evaluated by government and scientific agencies, including ATSDR, the National Academies of Sciences, Engineering, and Medicine (NASEM), and the United States Environmental Protection Agency (US EPA). 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 evidence is stronger than it truly is.

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.

ATSDR (2017a), which was written by one person over a period of 6 weeks concluded that "epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above," but "there is equipoise and above evidence for causation for TCE and Parkinson disease" based on "strong supporting mechanistic evidence." This conclusion is inconsistent with all other agency reviews, including the ATSDR Toxicological Profile, none of which concluded that TCE is a known cause of PD. No agency concluded that PCE, benzene, or vinyl chloride causes PD. The only agency review of *trans*-1,2-DCE I identified, ATSDR (2023b), did not discuss PD.

1.8 Plaintiffs' Experts' Opinions

Seven Plaintiffs' experts – Dr. Steven B. Bird (2024), Dr. Amelia K. Boehme (2024), Dr. Jason Cannon (2024), Dr. Lucio G. Costa (2024), Dr. Briana R. De Miranda (2024), Dr. Michael D. Freeman (2024), and Dr. Gary W. Miller (2024) – opined on whether evidence supports a causal association between TCE, PCE, benzene, and/or vinyl chloride and PD. The Plaintiffs' experts' causal conclusions are not supported by the scientific evidence.

Several of these experts relied heavily on ATSDR (2017a), which did not evaluate the evidence in a systematic, objective manner; used non-traditional methods and a biased framework to make determinations regarding causation; and has causal conclusions for many health outcomes, including PD, that are inconsistent with those of several other agency reviews. Even with these limitations, ATSDR (2017a) does not conclude that evidence for PD causation is equipoise or above for PCE, benzene, or vinyl chloride.

The Plaintiffs' experts' methodologies are not consistent with scientifically accepted methods for assessing causation (*e.g.*, Hill, 1965; Rodricks and Reith, 1998; Lewandowski and Rhomberg, 2005; US EPA, 2005; Lash *et al.*, 2021; Ward, 2009). These experts do not review available relevant epidemiology and experimental evidence systematically or objectively or consider how aspects of study quality impact the interpretation of results. They do not all interpret statistical significance appropriately or consider the relevance of experimental animal models to PD in humans.

All of these Plaintiffs' experts evaluate evidence to some degree in the context of the Bradford Hill (1965) considerations (*i.e.*, strength of association, consistency, specificity, temporality, dose-response, biological plausibility, coherence, experiment, and analogy), but these considerations often are not correctly applied or the evidence provided by the expert does not support his or her conclusion. It is particularly notable that several experts claim that TCE is analogous to PCE and other chemicals, despite there being considerable physiochemical, metabolic, and mechanistic differences between these chemicals that result in vastly different toxicological profiles. Even if evidence were sufficient to support any of these chemicals as a cause of PD,[1] it would not provide evidence for other chemicals.

Several Plaintiffs' experts compare the concentrations of TCE, PCE, benzene, and vinyl chloride in drinking water at Camp Lejeune to their respective maximum contaminant levels (MCLs), but none consider that these MCLs are not based on PD risk, and exceedance of an MCL does not provide evidence for an increased risk of PD.

Dr. Miller estimates exposures to TCE at Camp Lejeune in a misleading manner, and Dr. De Miranda's calculation of the potency of inhaled TCE relative to ingested TCE is simply wrong and inconsistent with the assumptions from Dr. Miller's calculation of exposures, as well as those of the National Research Council (NRC) (2009).

Finally, Dr. Bird concludes that evidence demonstrates that benzene and vinyl chloride are at least as likely as not to have caused PD at Camp Lejeune, in contrast to Dr. Freeman, who notes that evidence is below equipoise. Furthermore, most of these Plaintiff experts indicate that combined exposures to TCE, PCE, benzene, and vinyl chloride would result in more neurotoxicity than exposure to one solvent alone. Scientific evidence does not demonstrate that TCE, PCE, vinyl chloride, or benzene individually can cause PD, and each of these chemicals has a distinct MoA, targeting different cell types and operating through separate molecular pathways. Thus, exposure to a mixture of these of these chemicals would not be expected to exhibit a causal relationship with PD.

In summary, all of these Plaintiffs' experts opine on TCE, all but Dr. De Miranda opine on PCE, and Dr. Bird and Dr. Freeman discuss benzene and vinyl chloride. Their opinions are not all consistent, and some are contradictory. None of these experts conduct objective, rigorous, systematic evaluations of the scientific evidence that include an evaluation of study quality and the impact of study quality on the interpretation of results. As such, their discussions of the scientific evidence do not support their conclusions that there is sufficient evidence of causal associations or that causal associations are as least as likely as not.

[1] Evidence is sufficient for MPTP, but Plaintiffs' experts have not provided evidence for any other chemical in their reports.

1.9 Conclusions

Epidemiology studies of TCE, PCE, benzene, or vinyl chloride exposure and PD are not of high quality and most analyses do not provide evidence of associations. I did not identify any epidemiology studies of *trans*-1,2-DCE and PD. TCE animal studies do not provide evidence of causation, and no animal studies evaluated PCE, benzene, vinyl chloride, or *trans*-1,2-DCE and PD. Suggestions that a common metabolite of PCE and TCE may cause PD are not supported. 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 PD.

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, 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 I), 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 PD. 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 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 or other potential risk factors 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 or potential risk factor of interest, and each epidemiology study can have other limitations that can affect the interpretation of its results. That is, associations in epidemiology studies do not always indicate causation, as they could be a result of chance, bias, or confounding.[2]

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.

[2] 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 are also likely to smoke more than people who drink less alcohol, and not because drinking alcohol causes lung 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 Risk Ratio; OR = Odds Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio; 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.[3]

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

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

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

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

[3] 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).

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 ≥ ~ 2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size or the potential for biases. Conversely, we also recognized that statistical significance does not necessarily imply clinical or biological importance, particularly with larger than necessary sample sizes and other study elements that influence the reliability of estimated effects.

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

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

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

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

3.1.2 Study Design

There are several types of observational epidemiology study designs.[4] 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 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).

[4] 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, individual 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 non-exposed 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), an individual who was cured or died prior to the study is not included, which could affect study 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 (Künzli and Tager, 1997). 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, it is usually not possible to determine whether a particular exposure or treatment was a causal factor. Because of this limitation, I only briefly consider case reports or case series in this report.

Proportionate Mortality Studies

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

Pooled Analyses

A pooled analysis is a statistical analysis of individual data from primary studies (Blettner *et al*., 1999). A pooled analysis is often conducted to reconcile previous studies or may be prospectively planned, as part of the study protocol, to standardize data collection among several studies. With pooled analyses, new hypotheses may be examined or different sub-groups 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 can be low in a pooled analysis. 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 how much of a chemical one can be exposed to, 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).[5]

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

[5] 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 (NIOSH, 2017).

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.

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).

3.3 Individual Study Reviews

I first identified scientific studies from government and other agency reports that evaluated TCE, PCE, benzene, vinyl chloride, and *trans*-1,2,-DCE and PD for various purposes. I also conducted literature searches using PubMed and Scopus for studies published after these agency literature searches were completed and reviewed reference lists of identified studies (Attachment A). I summarized relevant information on study characteristics and results, as well as study quality, in text and tables.

I evaluated study quality to determine how valid and reliable the results of individual studies are for addressing causation. As suggested by Savitz *et al*. (2019), rather than consider all possible aspects of study quality, I identified the few critical aspects that warranted detailed assessment based on their potential impact on study validity, and considered other aspects of quality less formally. The study quality criteria I used are based on those identified from several available frameworks for evaluating study quality (*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 toxicity study, I assessed the strengths and limitations for each critical quality aspect presented in Sections 3.3.1 and 3.3.2, respectively.

Camp Lejeune epidemiology studies are reviewed in Section 5. TCE, PCE, benzene, and vinyl chloride epidemiology studies are reviewed in Sections 6.1, 7.1, 8.1, and 9.1, respectively, and TCE, PCE, benzene,

and vinyl chloride toxicity studies are reviewed in Sections 6.2, 7.2, 8.2, and 9.2, respectively. I review 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	▪ 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
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	▪ 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, smoking, alcohol, or other potential occupational exposures/other chemical exposures ▪ ≤ 5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Considered time-varying nature of relevant covariates	▪ Did not control for or consider age, sex, smoking, alcohol, or other potential occupational exposures/other chemical exposures ▪ > 5% or unknown amount of missing data that were not appropriately addressed ▪ Did not consider time-varying nature of relevant covariates
Temporality	▪ Exposure measured or documented before the outcome ▪ Appropriate consideration of latency (lag ≥ 5 years or exclusion of cases occurring ≤ 5 years after exposure)	▪ Exposure not measured or documented before the outcome ▪ No/insufficient consideration of latency (< 5 years)

Notes:
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). 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 nondiseased (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 chemical exposure, 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 chemical exposures, the presence of a chemical in drinking water, 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).[6] 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.

A JEM is more reliable than some other means of estimating exposure, but the quality of an exposure assessment based on a JEM varies based on the expertise of the person(s) linking job titles to exposures, and whether the assessment is semi-quantitative or not (*e.g.*, whether duration or intensity of exposure is considered). Also, exposure estimates based 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. While studies that estimate 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 are of higher quality than those that do not, 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 rely on JEM or job titles more generally do not reflect actual individual exposure levels.

A directly measured or modeled chemical in drinking water with no water consumption data, as reported in the Camp Lejeune studies, is not a high-quality exposure measurement. In contrast, a chemical directly measured in drinking water that is linked to robust water consumption data can be a high-quality direct exposure measurement. Modeled chemical concentrations in drinking water based on chemical measurements in groundwater could similarly provide quality exposure data when linked to water consumption data; however, the quality and accuracy of estimates of drinking water modeled from groundwater rely on the accuracy of the chemical measurement and model assumptions. In addition, chemical measurements or estimates in drinking water or groundwater that reflect contamination levels at 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.*, TCE and PCE in 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

[6] 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.

risks of particular chemical exposures. 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).

Self-reported exposure information is subject to potential recall inaccuracy due to the long time periods between chemical use or exposure and interviews, and potential recall bias in case-control studies. Also, exposure estimates based solely on the presence of a chemical in drinking water and residential proximity to chemically contaminated sites do not take into account individual exposure variations due to behavior or environmental differences (*e.g.*, people drink different amounts of tap water at home), and thus do not provide reliable exposure estimates for any individual.

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, 2011a, 2012). TCE and PCE that are not quickly exhaled can be metabolized to breakdown products and excreted in the urine (ATSDR, 2019b; US EPA, 2011a, 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 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, 2023a).

With respect to missing data, studies that are missing exposure data on < 5% of the study population (Jakobsen *et al*., 2017) or that use appropriate analytical methods to address the missing exposure data (*e.g.*, multiple imputation [Perkins *et al*., 2018]) are stronger than studies that have ≥ 5% missing data and do not account for missing data with appropriate methods.

Assessments of chemical exposure levels are stronger than assessments that only consider whether a participant was ever exposed to a chemical at any level. Similarly, studies that take into consideration the duration, intensity, or time-varying nature of exposure are stronger than those that do not.

Finally, self-reported exposure information is subject to potential recall inaccuracy, particularly when it occurs long after the exposure was reported to have occurred. It is also subject to bias, particularly in case-control studies, when cases and controls may systematically recall prior exposures differently.

Outcome Assessment

Studies that include a diagnosis or confirmation of PD by a medical professional, a histological evaluation, or a disease registry provide stronger outcome data than studies that rely on self- or proxy-reports of disease because the latter are more likely to be subject to misclassification.

Because PD is usually not fatal, studies that evaluated PD mortality are weaker than those that evaluated PD incidence (Johns Hopkins Medicine, 2024; PFNCA, 2021; Coggon *et al*., 1997). Also, data from death certificates are not always reliable; for example, contributing causes of death may not always be reported (McGivern *et al*., 2017).

Covariates Considered

A covariate is an independent variable that can influence the outcome of interest, but which is not of direct interest itself; it may be a confounder but does not have to be (Portia, 2014). Age, sex, genetic factors/family history, and heavy alcohol intake are PD risk factors (Mayo Clinic, 2020), while smoking is inversely associated with PD (APDA, 2018). All of these factors should be considered as potential confounders in studies of PD, 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 therefore considered studies to be stronger if they controlled for at least some of these factors in the study design or analysis. I am not aware of any confirmed chemical confounders of PD, but dry cleaners and other industrial occupation exposure groups were likely exposed to other chemicals, including other solvents, in addition to TCE, potentially impacting any reported associations between TCE and PD. As such, stronger studies consider other potential chemical exposures and additional risk factors in analyses.

Studies that assessed covariates that can vary over time (*i.e.*, 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

Studies that measured or documented exposures prior to diagnoses are of higher quality than those that measured or documented exposures at the time of or after diagnoses, as the former are more likely to have appropriately captured the temporal relationship between the exposure and outcome (Gordis, 2014). Studies with an insufficient duration of time between the exposure and the outcome with respect to disease development (< 5 years) are weaker than those with sufficient time between the exposure and PD (≥ 5 years) (Hustad and Aasly, 2020).

3.3.2 Toxicity Studies

Studies in rodents are classified based on duration as acute (less than 24 hours), subacute (1 month or less, although most are 28 days), subchronic (1 to 3 months, although most are 13 weeks), and chronic (typically 6 months to 2 years) (Aleksunes and Eaton, 2019; OECD, 2024).

I assessed animal study strengths and weaknesses based on several formal quality and risk-of-bias frameworks: the Integrated Risk Information System (IRIS) (US EPA, 2022; NRC, 2014), the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) (NTP, 2019), the Science in Risk Assessment and Policy (SciRAP) (Molander *et al*., 2014), and the "Animal Research:

Reporting of *In Vivo* Experiments" (ARRIVE) framework (Percie du Sert *et al*., 2020; Batke *et al*., 2023). 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). For example, OECD Guidelines state that subchronic studies should test at least 10 male and 10 female rodents per dose, and that subacute studies should test at least 5 male and 5 female rodents per dose (OECD, 2024). I did not systematically review *in vitro* data.

In Table 3.3, I summarize the key aspects of the quality domains I considered for animal toxicity studies:[7] 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.

Table 3.3 Animal Study Quality Evaluation Criteria

Parameter	Strength	Weakness
Reporting	For each outcome, report: (1) 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.	Did not report all of these aspects.
Allocation	Random allocation of animals to experimental groups.	Did not specify whether allocation to experimental groups was random.
Bias	No indication that there were differences across treatment groups that could bias results (*e.g.*, co-exposures, vehicle, diet, gavage error, palatability, husbandry, health status).	Variables not adequately balanced across experimental groups, potentially biasing the results.
Sample	Adequate sample size; all animals were accounted for throughout the study.	Inadequate sample size; animals not all accounted for throughout the study.
Chemical Administration and Characterization	Chemical source, purity, and composition were adequate, chemical purity was independently verified, and steps taken to ensure reported exposure levels were accurate.	Chemical source, purity, or composition were inadequate, chemical purity was not independently verified, or no steps 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; the exposure period included the critical window of sensitivity; and the duration of exposure was adequate 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; the exposure period did not include critical window of sensitivity; or the duration of exposure was inadequate 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

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

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 do 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 toxicity 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.

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 toxicity 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.

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.

3.3.3 Study Quality and Human Relevance Evaluation

For both epidemiology and animal studies, because the cutoffs for higher or lower quality are subjective, I did not simply categorize studies as higher or lower quality, but rather reviewed each study with the above study quality aspects in mind, and determined how each aspect impacted the interpretation of both individual study results and the body of literature as a whole. Because some epidemiology study designs are inherently lower quality and limited in terms of the information that they can provide regarding causal inferences (*e.g*., case reports), I conducted formal quality assessments of cohort and case-control studies only. I conducted quality assessments of relevant toxicity studies, discussed below.

Study quality criteria for animal 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 the animal study results have human relevance (Aleksunes and Eaton, 2019). If a study has poor internal validity, then it cannot have external validity. Thus, I conclude 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 results) have limited human relevance. Also, by design, animal toxicity studies test high doses that are generally not directly relevant to human environmental or occupational exposures (Goodman *et al*., 2020). As noted by NRC (2009) in its report, "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects," "for equivalent inhalation exposures to TCE and other VOCs, internal doses are substantially higher in rodents than in humans (Bruckner *et al*., 2008)." NRC (2009)

further stated, "Mice and rats absorb more inhaled TCE and PCE, metabolically activate more of their absorbed dose, and inactivate epoxide metabolites less efficiently than do humans." Since rodents have substantially greater effects from exposures to chemicals via inhalation relative to humans, caution is warranted with respect to interpreting any potential relevance to humans (NRC, 2009).

I considered animal toxicity 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. I considered them to have no human relevance if they did not examine the outcome of interest.

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 PD particularly with respect to epidemiology, animal toxicity, 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 a risk estimate between 1 and 1.3 as a slight positive association, from 1.3 to < 2 as a positive association, from 2 to < 3 as a moderately strong association, and > 3 as a strong association. I am not aware of any framework that suggests a risk estimate of 1.1 as being strong, except for ATSDR (2017a), discussed in Section 3.6.2. 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 and free of confounding and bias) is a causal association supported. If studies are of low quality or if results are generally not consistent, then it is more likely that positive associations are a result of chance, bias, or confounding, and the available evidence does not support causation.

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.

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 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 effect is sufficient to lead to cancer, or if the effect is something common to carcinogens and noncarcinogens, this should not be considered as 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:

> 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? (Hill, 1965)

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 6.5, 7.5, 8.5, and 9.5, respectively, to evaluate whether the evidence as a whole supports causation. Too few studies were available to conduct this type of assessment for *trans*-1,2-DCE.

3.5 Agency Reviews

Health risks from chemicals are regularly evaluated by several government and scientific agencies, including ATSDR, NASEM, and US EPA. 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). Some Toxicological Profiles have a dozen authors and three peer-reviewers. All Toxicological Profiles consider public comments as part of the review process.

In contrast, the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) was written by one author (Dr. Bove) over a period of 6 weeks (Bove, 2024a), and was peer reviewed by two people, one of whom "didn't like it," according to Dr. Bove (2024a). This assessment did not evaluate the evidence in a systematic, objective manner, and used non-traditional methods and a biased framework to make determinations regarding causation. ATSDR (2017a) said that its framework for evaluating causation is based on the Institute of Medicine (IOM) framework shown in Table 3.4. However, a comparison of the two frameworks shows that for each category, IOM (2008) requires more scientific evidence than ATSDR (2017a) does (Table 3.5). This results in ATSDR (2017a) concluding that there are causal relationships for many health outcomes that are inconsistent with those of several other agency reviews, including for PD.

Like IOM (2008) and ATSDR (2017a), most agencies use some type of framework to evaluate the scientific evidence. These frameworks are generally designed to inform policy-based decisions.

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

Table 3.5 Categories for the Level of Evidence for Causation

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

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

Level of Evidence	IOM (2008)	ATSDR (2017a)
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.

4 PD

PD is a progressive neurodegenerative disease that affects movement (Mayo Clinic, 2020; Stoker and Greenland, 2018). A prodromal (*i.e*., pre-motor) period often precedes clinical motor symptoms for up to 12-14 years prior to diagnosis of PD (Stoker and Greenland, 2018). The symptoms that are associated with the prodromal phase of PD include olfactory dysfunction (*e.g*., hyposmia), constipation, and rapid eye movement sleep disorders (Stoker and Greenland, 2018). Although some dopaminergic neuron loss occurs during the prodromal stage, none of these symptoms are specific to PD.

The early signs of clinical PD include a barely noticeable tremor in one hand, stiffness or slowing of movement (*i.e*., bradykinesia), little or no facial expression, not swinging the arms when walking, and soft or slurred speech (Mayo Clinic, 2020). Early symptoms often occur only on one side of the body (Stoker and Greenland, 2018). Other symptoms include rigid muscles, impaired posture and balance, loss of automatic movements (*e.g*., blinking, smiling), reduced sense of smell, and writing changes (*i.e*., micrographia) (Mayo Clinic, 2020). The diagnosis of PD is primarily made based on clinical symptoms (*i.e*., a resting tremor, bradykinesia, and rigidity) (Stoker and Greenland, 2018).

Parkinsonism (also called Parkinsonian disorders) describes a collection of signs and movement-related symptoms that are associated with several conditions, including PD (Parkinson's Foundation, 2025). While PD is a type of parkinsonism, the symptoms of parkinsonism are not specific to PD, and several other conditions have similar symptoms. The signs of parkinsonism include bradykinesia, stiffness or rigidity, resting tremor, and impaired postural reflexes (Parkinson's Foundation, 2025; Elbaz *et al*., 2002). Primary parkinsonism is a group of progressive neurological disorders that includes atypical parkinsonism and PD (Parkinson's Foundation, 2025). Atypical parkinsonism, sometimes called Parkinson's plus syndromes, comprises several conditions, including multiple system atrophy, progressive supranuclear palsy, and dementia with Lewy bodies. Atypical parkinsonism is characterized by a faster progression of disease compared to PD (Parkinson's Foundation, 2025). Secondary parkinsonism has symptoms similar to PD but can be caused by several factors, including, but not limited to, brain tumors, exposure to toxicants, or taking certain medications (Parkinson's Foundation, 2025). Unlike PD symptoms, secondary parkinsonism symptoms may improve or resolve with or without treatment (Parkinson's Foundation, 2025).

The prevalence of PD is approximately 0.5-1% among those aged 65-69 and 1-3% among those ≥ 80 years old (Stoker and Greenland, 2018). Pringsheim *et al*. (2014) reported that, worldwide, PD prevalence (per 100,000) in different age groups were 41 for people aged 40-49, 107 for people aged 50-59, 173 for people aged 55-64, 428 for people aged 60-69, 425 for people aged 65-74, 1,087 for people aged 70-79, and 1,903 for people aged > 80. Goldman (2014) reported that up to one million people in the US have been diagnosed with PD and that 50,000-60,000 new cases are diagnosed annually.

PD is caused by the impairment or death of dopaminergic neurons (*i.e*., brain cells that produce dopamine) located in the SNpc of the basal ganglia (the basal ganglia is an area in the brain that controls movement) (NIH, 2017). When the dopaminergic neurons of the SNpc are impaired or die, dopamine levels in the basal ganglia are lower, resulting in the movement problems that characterize PD (Mayo Clinic, 2020; NIH, 2017).

The underlying mechanisms that cause a loss of dopaminergic neurons in SNpc and lead to PD are not known, but several pathological outcomes at the cellular level have been identified. For example, in humans diagnosed with PD and laboratory animal studies of PD, α-synuclein, an abundant protein in dopamine-

producing nerve cells, misfolds and aggregates into clumps called Lewy bodies. The aberrant overaccumulation of α-synuclein is hypothesized to contribute to PD pathogenesis (Gaig and Tolosa, 2009). In addition, studies using the toxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which inhibits complex I of mitochondria of dopaminergic neurons in SNpc, identified mitochondrial dysfunction as playing a role in PD.

Still, the exact causes and risk factors for PD are largely unknown and the biological processes that result in the development of the condition are complex and not well understood (Gaig and Tolosa, 2009). Identified risk factors include older age, specific genetic mutations, a family history of PD, being male, and, possibly, exposure to certain environmental factors (Mayo Clinic, 2020; Stoker and Greenland, 2018; Marras *et al*., 2019; Noyce *et al*., 2012).

Clinical symptoms of PD only become apparent in humans later in the course of the disease, after SNpc dopamine levels have been depleted by an estimated 70-80% (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Fearnley and Lees, 1991) and a significant amount of SNpc dopaminergic neurons have been lost or impaired (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024).

The available literature reports a broad range regarding the magnitude of dopaminergic neuron loss required to produce clinical signs of PD in humans. Some estimates range from 30% to 50%, but most are at least 50% and generally range from 60% to 80% (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). According to the National Institute of Neurological Disorders and Stroke (NINDS) (NIH, 2024), "By the time Parkinson's is diagnosed, most people have lost an estimated 60 to 80 percent of their dopamine-producing cells in the *substantia nigra*." Fearnley and Lees (1991) reported 48% loss of neurons in the SNpc, but 68% neuronal loss within the lateral ventral tier region of the SNpc (the lateral ventral tier is the region most vulnerable to neuron loss in PD) at the onset of PD symptoms. Hirsch *et al*. (1988) reported a "massive" 77% loss of dopaminergic neurons based on autopsies of patients with PD. Similarly, Zarow *et al*. (2003) reported 77.8% neuronal loss in the SNpc patients with pathologically confirmed PD.

Finally, in an umbrella review of PD,[8] Bellou *et al*. (2016) reviewed 38 articles that included 75 unique meta-analyses published between 2005 and 2015. The meta-analyses evaluated a wide range of potential risk factors, which the authors sorted into categories, such as biomarkers, dietary factors, drugs, exposure to environmental agents, habits, and medical history/comorbidities (Bellou *et al*., 2016). The strongest evidence was for constipation and physical activity, followed by anxiety or depression, beta-blockers, head injury, serum uric acid, and smoking, although the authors noted that associations with these latter factors were not as convincing.

[8] According to Bellou *et al*. (2016), an umbrella review is "a systematic collection and evaluation of multiple systematic reviews and meta-analyses performed on a specific research topic."

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. I identified four cohort studies that evaluated PD risks in US Marines and Navy personnel or civilian employees at Camp Lejeune. The characteristics, results, and quality of these studies are detailed in Attachments B and C. Below, I provide brief summaries of the studies and describe important quality considerations that impact the interpretation of study results, followed by a discussion of the study results.

5.1 Bove *et al*. (2014a)

5.1.1 Overview

Bove *et al*. (2014a) retrospectively evaluated PD deaths among 4,647 civilian employees who began full-time employment at Camp Lejeune between April 1973 and December 1985. For comparison, the authors established a cohort of 4,690 civilian employees who met the same criteria at Camp Pendleton but were not employed at Camp Lejeune between April 1973 and December 1985. Individuals at both bases had similar types of occupations, but Camp Pendleton did not have a contaminated drinking water supply (ATSDR, 2008). The median age at the start of follow-up was 31 years for those employed at Camp Lejeune and 34 years for those employed at Camp Pendleton. Both cohorts were followed for a maximum of 30 years, from January 1, 1979 (or the start of employment, whichever was later), to December 31, 2008 (if the person was known to be alive, or to the date of death or the date the person was last known to be alive).

Bove *et al*. (2014a) ascertained chemical-specific exposures through a historical reconstruction of the spatial and temporal distribution of contaminants (ATSDR, 2007a, 2013a). ATSDR (2007a, 2013a) used groundwater fate and transport and distribution system models to compute monthly average estimates of concentrations of contaminants in the Hadnot Point distribution system. According to Bove *et al*. (2014a), Hadnot Point supply wells served the main area of the base, where most workplaces were located, until those wells were shut down in early February 1985. Exposure to contaminated drinking water occurred only on base and not at civilian worker residences off base. No data on water consumption (*e.g*., by drinking, cooking, doing laundry, showering, or swimming) on base were available. The median length of employment during 1973-1985 for employees in the Camp Lejeune cohort was about 2.5 years.

Bove *et al*. (2014a) ascertained vital status through linkage of personal identifier information from the Defense Manpower Data Center (DMDC) database to data from the Social Security Administration (SSA) Death Master File, SSA Office of Research, Evaluation and Statistics (ORES) Presumed Living Search. Of the combined Camp Lejeune and Camp Pendleton cohorts, almost 50% of study participants were reportedly not able to be uniquely matched to the ORES file or their vital status was listed as "unknown." For those individuals, a commercial tracing service was used to obtain information on vital status. Identified deaths and individuals whose vital status remained unknown were then searched in the National Death Index (NDI). If vital status remained unknown after the NDI search, those participants were considered lost to follow-up. Underlying and contributing causes of death information were obtained from NDI Plus.

Between 1979 and 2008, Bove *et al*. (2014a) observed only five PD deaths in the Camp Lejeune cohort, which is reflected in the wide CIs of risk estimates. The authors computed a SMR and 95% CI comparing the Camp Lejeune and Camp Pendleton cohorts to the age, sex, race, and calendar period-specific US mortality rate. The authors found no statistically significant evidence of an increased PD mortality risk among Camp Lejeune civilian employees compared to what was expected based on rates in the US general population (SMR = 2.19, 95% CI: 0.71-5.11).

In comparisons of PD mortality between the Camp Lejeune and Camp Pendleton cohorts, Bove *et al*. (2014a) relied on Cox extended regression models with age as the time variable and base location as a time-varying dichotomous variable to calculate HRs. No statistically significant difference in mortality rates was observed when Camp Lejeune civilian employees were compared to civilian employees at Camp Pendleton (HR = 3.13, 95% CI: 0.76-12.86), after implementing a 10-year lag that was selected based on Akaike's information criterion (AIC).

Within the Camp Lejeune cohort, Bove *et al*. (2014a) evaluated exposure-response relationships based on cumulative exposures to drinking water contaminants using Cox extended regression models with age as the time variable and cumulative exposure as a time-varying variable. Cumulative exposures (µg/L-years) were based on monthly average contaminant concentrations in the Hadnot Point water system and dates of employment at Camp Lejeune. Because cumulative exposures to contaminants were correlated, each model included only one contaminant at a time. To identify potential confounding, the authors required that the covariate change the risk estimate by 10%. The final Cox models included sex, race, occupation (blue collar *vs.* white collar), and education level.

Bove *et al*. (2014a) did not observe a statistically significant increase in risk among employees with maximum cumulative exposures ≥ median for TCE (HR = 2.51, 95% CI: 0.21-30.76), PCE (HR = 2.68, 95% CI: 0.22-33.28), benzene (HR = 2.52, 95% CI: 0.20-31.59), or vinyl chloride (HR = 2.81, 95% CI: 0.23-34.11) when compared to those with maximum cumulative exposures < median after implementing a 10-year lag. In addition, the authors evaluated exposure-response relationships using both continuous and $\log_{10}$ continuous cumulative exposure models. The log transformed data provided a better model fit and better captured the exposure-response relationship. There was no increased risk of PD mortality associated with any chemical in the log-transformed models.

5.1.2 Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 2%), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the study, less than 15% of the study population had died, and only a small number of PD deaths were observed (n = 5), which resulted in wide CIs and limited the precision of the estimated associations.

Exposure Assessment. In external comparisons to the US and Camp Pendleton populations, there was no consideration of chemical-specific exposures or doses. Potential exposures used for comparisons within the Camp Lejeune cohort were estimated based on groundwater fate and transport models of the monthly average concentrations of chemicals in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. These direct measurements are more reliable than exposure estimates that are not based on any quantitative information, but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely. In a recent deposition, Bove (2024a) acknowledged the uncertainty regarding the assessment of time spent at the main area served by Hadnot Point, the lack of information on water consumption, and that the assumption that all workers lived off base was incorrect.

Outcome Assessment. The study assessed PD mortality, which is a serious limitation because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e.*, SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for age and sex in the US comparison, and age, sex, and occupation (blue *vs.* white collar) as a proxy for other chemical exposures in the Camp Pendleton and internal comparisons. The authors did not consider or control for other potential occupational exposures in the external comparison to the US population, genetic factors, a family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly, it is unclear if they analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

5.1.3 Conclusion

Bove *et al*. (2014a) did not observe statistically significant associations between being a civilian employee at Camp Lejeune and PD mortality in comparisons with the US mortality rate and the Camp Pendleton cohort. In chemical-specific analyses based on maximum cumulative exposures within the Camp Lejeune cohort, no changes in risk were reported for dichotomous (≥ median *vs.* < median) or continuous log-transformed exposures. These analyses were all based on only five individuals who died of PD at Camp Lejeune, making results difficult to interpret. Most importantly, although the study was able to rely on direct chemical exposure assessments, the authors were not able to account for important exposure information (*e.g.*, ingestion rates) to accurately assess individual exposure, and all chemical exposures were highly correlated with each other, limiting any chemical-specific conclusions. The study also failed to incorporate all relevant covariates, which may have resulted in some confounding bias. Overall, this study does not provide evidence for an association between TCE, PCE, benzene, or vinyl chloride and PD mortality.

5.2 ATSDR (2018b)

5.2.1 Overview

ATSDR (2018b) retrospectively evaluated PD incidence among 50,684 Marines and Navy personnel stationed anytime between April 1975 and December 1985 and 2,168 civilian employees employed anytime between October 1972 and December 1985 at Camp Lejeune. For comparison, the authors established a cohort of 8,615 Marines and Navy personnel and 1,425 civilian employees who met the same criteria at Camp Pendleton but could not have lived or worked at Camp Lejeune during the period of drinking water contamination.[9] According to the authors, Camp Pendleton did not have VOC-contaminated drinking water during the period evaluated in this analysis. The median age at the end of follow-up (at survey or death) was 50-54 for Marines and Navy personnel at both bases, 60-64 for civilian employees at Camp Lejeune, and ≥ 65 for civilian employees at Camp Pendleton. Marines and Navy personnel were followed for a maximum of 38 years, from April 1975 to 2012, and civilian employees were followed for a maximum of 40 years, from October 1972 to 2012.

ATSDR (2018b) ascertained chemical-specific exposures through a historical reconstruction of the spatial and temporal distribution of the drinking water contaminants at Camp Lejeune using groundwater fate and transport distribution models (ATSDR, 2007a, 2013a). The modeling provided monthly average estimates of contaminant concentrations in drinking water delivered to residences or workplaces from the Tarawa Terrace, Hadnot Point, and Holcomb Boulevard water treatment plants.

For Camp Lejeune Marines and Navy personnel, ATSDR (2018b) relied on the DMDC database and historical information supplied by the DMDC and US Marine Corps (USMC) to identify units stationed at either base and to initially identify those stationed at Camp Lejeune and those stationed at Camp Pendleton. Exposure assessment was based on estimated contaminant levels in the drinking water serving the Marines' or Navy personnel's residence. Residential history information, DMDC data, and base family housing records were also used to make any corrections to exposure history.

ATSDR (2018b) assumed that civilian workers were employed at their respective bases during the entire quarter they were listed in the DMDC database. Information from Camp Lejeune current staff and retired base personnel indicated that most workplaces were located in the main area of the base served by the Hadnot Point water treatment plant. Therefore, the authors assumed all civilian workers received water from the Hadnot Point system.

The Office of Management and Budget (OMB)-approved health survey used by ATSDR (2018b) collected information on cancers and diseases of interest (including PD), residential history at each base, and lifestyle and demographic factors. 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). Self-reported cases were confirmed by medical records or death certificates.

Between 1979 and 2008, ATSDR (2018b) observed 78 PD cases among Marines and Navy personnel and 20 PD cases among civilian employees at Camp Lejeune. Based on an unconditional logistic regression

[9] ATSDR (2018b) analyzed Marine and Navy personnel and civilian employee cohorts, as well as ATSDR 1999-2002 survey respondents (described in Ruckart *et al*. [2013]), which included Marines and their spouses and children. The 1999-2002 survey was conducted to investigate health outcomes in children born at Camp Lejeune before 1985. Marines who responded to the 1999-2002 survey who were stationed at Camp Lejeune after March 1975 were included in the Marine cohort in ATSDR (2018b). Marines stationed at Camp Lejeune before March 1975 and their spouses and children were analyzed separately in ATSDR (2018b), because there was no available comparison group, so the results were necessarily qualitative, and are not included in my report.

analysis, a similar risk for PD incidence was demonstrated in Camp Lejeune Marines and Navy personnel when compared to Camp Pendleton (OR = 0.89, 95% CI: 0.51-1.55). However, civilian employees at Camp Lejeune had an increased risk when compared to employees at Camp Pendleton (OR = 3.11, 95% CI: 1.16-8.32).

In chemical-specific analyses, ATSDR (2018b) categorized exposures as low, medium, and high according to 50th and 90th percentile cut points, except for female Marines and Navy personnel, for whom cut points were based on the 75th and 90th percentile, as the 50th percentile corresponded to an exposure of 0 µg/L-mos. For Marines and Navy personnel, the authors also reported that categorized levels of TCE, benzene, vinyl chloride, and total VOCs were almost completely correlated ($\gamma = 0.99$), so results were only presented for TCE and PCE ($\gamma = 0.88$). To identify potential confounding, the authors required that the covariate change the risk estimate by 10%. Only sex was included in models for Marines and Navy personnel.

When compared to those at Camp Pendleton, ATSDR (2018b) reported that Marines and Navy personnel at Camp Lejeune did not have any changes in the risk of PD incidence with increasing cumulative exposure to TCE (OR range: 0.29-0.87). Similarly, there were no changes in the risk of PD incidence when comparing those with medium (110 to < 11,030 µg/L-mos) or high (≥ 11,030 µg/L-mos) TCE exposures to those with low (< 110 µg/L-mos) exposure in the Camp Lejeune cohort (OR range: 0.33-1.00), but no p-trends were reported.

When considering PCE exposures, ATSDR (2018b) reported no change in PD risk among Marines and Navy personnel at Camp Lejeune when compared to Camp Pendleton (OR range: 0.54-1.22). A statistically significant *decrease* in PD risk was observed among Camp Lejeune Marines and Navy personnel with medium cumulative exposure (36 to < 711 µg/L-mos OR = 0.57, 95% CI: 0.34-0.87), but not among those with high exposures (≥ 711 µg/L-mos OR = 1.32, 95% CI: 0.70-2.49), when compared to those with low (> 0 to < 36 µg/L-mos) exposures at Camp Lejeune.

According to ATSDR (2018b), the correlation between TCE and PCE in the civilian exposure estimates was approximately equal to one, so results were only reported for TCE and PCE combined. The authors did not control for any covariates in chemical-specific analyses among civilian employees. When compared to civilian employees at Camp Pendleton, employees at Camp Lejeune had an increased risk for PD incidence with medium levels of cumulative exposure (OR = 3.47, 95% CI: 1.18-10.22), but not with low (OR = 2.78, 95% CI: 0.87-8.94) or high (OR = 2.86, 95% CI: 0.67-12.13) levels. In analyses comparing those with medium and high cumulative exposures in Camp Lejeune to those with low exposures, no associations were reported (OR range: 1.81-2.03) though the authors report a positive monotonic exposure-response relationship but did not report a p-trend.

5.2.2 Quality Considerations

Study Population. This study used appropriate comparison groups, but selection bias was likely. 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 authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

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

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

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

Also, there were a small number of PD cases in the civilian population (n = 20), which may have resulted in risk estimates with reduced precision.

Exposure Assessment. In external comparisons of the Camp Lejeune populations to the Camp Pendleton populations, there was no consideration of chemical specific exposures or doses, or even water ingestion rates. Analyses integrating chemical-specific exposures used reconstructed exposures based on groundwater fate and transport and water distribution system models coupled with historical occupation codes, period and duration of employment or residence, and workplace or residence location. These direct measurements are more reliable than exposure estimates that are not based on any quantitative information (*e.g.*, assignment on base), but without a direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption/exposure data), it is still likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures 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 exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Finally, there was a high correlation between the categorical variables for TCE, benzene, vinyl chloride, and total volatile organic compounds (TVOCs) in the ATSDR (2018b) study, which limits the interpretation of chemical-specific results.

In a deposition, Dr. Bove (2024a) states, "The Marine Corps…didn't know, where barracks were on base, where units were barracked on base. And we relied on CAP [community assistance panel] members plus people they knew who had that memory…" Dr. Bove (2024) also stated that they were not able to take into account a Marine's deployment off base and so they assumed that the DMDC data represented a continuous presence at Camp Lejeune, raising more concerns over 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al.*, 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al.*, 1991) or multiple exposure categories (Dosemeci *et al.*, 1990; van Smeden *et al.*, 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed

that nondifferential exposure measurement error could lead to bias towards or away from the null in a recent deposition, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

Outcome Assessment. Cases were confirmed using medical records or death certificates, but initial reliance on self-reported cases could have resulted in some missed cases. This analysis also focused on PD incidence, which is more informative than analyses evaluating mortality, since PD is not a fatal disease.

Covariates Considered. The authors controlled for sex in some analyses but not others, and considered but did not control for age, smoking, alcohol, or other potential occupational exposures or chemical exposures in all analyses because adjusted results differed from unadjusted results by less than 10%. The authors did not consider or control for genetic factors or family history of PD. Covariate data were collected at a single timepoint *via* self-report and smoking, alcohol consumption, and other occupational exposures were missing for more than 5% of participants, increasing the likelihood of biased results.

Temporality. The study exposure and outcome periods overlapped, with follow-up beginning coincident with first exposure *(i.e.*, exposures could continue to occur after follow-up began). Some participants were followed for up to 40 years, but the authors did not consider a latency period.

5.2.3 Conclusion

ATSDR (2018b) observed a statistically significant relationship between civilian employment at Camp Lejeune and PD incidence, when compared with Camp Pendleton civilian employees, and a statistically significant increase in risk was observed among Camp Lejeune civilian employees with medium TCE and PCE exposure when compared with Camp Pendleton employees. However, there were no associations in analyses of employees with high exposures compared to Camp Pendleton, or internal Camp Lejeune analyses based on levels of exposure, and a *decrease* in PD incidence risk was observed among Camp Lejeune Marines and Navy personnel with medium PCE exposure when compared to those with low exposure. No other associations were observed among Marines and Navy personnel. This study has many potential limitations, including selection bias, nondifferential exposure measurement error, outcome bias, confounding bias, and latency bias. The inconsistent results and major study limitations indicate that this study does not provide sufficient evidence for an association between TCE, PCE, benzene, or vinyl chloride exposure and PD incidence.

5.3 Goldman *et al*. (2023)

5.3.1 Overview

Goldman *et al*. (2023) compared the risk of PD incidence in 84,824 Marines and Navy personnel stationed at Camp Lejeune to 73,298 Marines and Navy personnel stationed at Camp Pendleton in a semi-ecological analysis (*i.e.*, all participants at each base were assigned the same ecological exposure value, but individual outcomes were considered). Similar to prior studies, the authors only considered Marines and Navy personnel stationed at Camp Lejeune or Camp Pendleton between April 1975 and December 1985. In this study, however, personnel who served at both locations were assigned to the Camp Lejeune cohort and were not excluded. In addition, all personnel must have been stationed at either base for at least 3 months to be included. Personnel were identified from the DMDC Active Duty Military Personnel Master File and USMC, and an analytic cohort was constructed based on individuals who ever use Veterans Health Administration (VHA) or Medicare health care services.

Among those veterans who used VHA services, Goldman *et al*. (2023) searched Corporate Data Warehouse Outpatient, Inpatient, and Community Care files for PD diagnoses between January 1, 1999, and February 17, 2021. The authors also identified other forms of neurodegenerative parkinsonism, including multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies (DLB), and corticobasal degeneration, as well as prescriptions for dopaminergic medications. Individuals were classified as having probable or possible PD based on the consistency and duration of clinical records indicating a PD diagnosis. A similar approach was used to ascertain cases in Medicare files, including outpatient claims and inpatient and skilled nursing facilities claims from January 1, 1997, through December 31, 2018, and pharmacy claims from January 1, 2006, through December 31, 2018. Prodromal PD symptoms were also extracted from medical records. Camp Lejeune veterans had a higher usage of the VHA (46.1%) compared to those at Camp Pendleton veterans (40.0%) although it was not clear if these rates were statistically different. The mean age at the end of follow-up was about 60 years for both cohorts.

Goldman *et al*. (2023) reported that 279 Camp Lejeune veterans and 151 Camp Pendleton veterans had possible or probable PD. Based on an unconditional logistic regression analysis, an increased risk of possible or probable PD incidence among Camp Lejeune Marines and Navy personnel was observed when compared to Camp Pendleton Marines and Navy personnel, after controlling for age, sex, race, and ethnicity (OR = 1.70; 95% CI: 1.39-2.07). Incorporating smoking status (*i.e*., ever or never) or military rank (*i.e*., officer or enlisted) into the model did not substantially impact results, however, smoking status was unknown for > 25% of each cohort. Similar results were also found in sensitivity analyses that included only those active VHA users prior to PD diagnosis, those with probable PD, or those with diagnoses of PD or DLB. However, in an analysis restricted to PD ascertained before January 13, 2017 (*i.e*., the date of the government ruling on presumptive service-connection for eight diseases associated with the contaminated water), the association was attenuated and no longer statistically significant (OR = 1.28, 95% CI: 1.00-1.64). No associations were found for other forms of neurodegenerative parkinsonism, but several associations were reported for prodromal symptoms (*e.g*., anxiety) in veterans without PD. None of these prodromal symptoms alone or combined are specific for PD.

5.3.2 Quality Considerations

Study Population. The authors used appropriate comparison groups, however, greater than 50% of both cohorts had to be excluded because they did not receive medical care through the VHA or Medicare. It was not clear how cohort members who received care from the VHA or Medicare differed from those who did not. Although selection bias was likely in the main analysis due to the known contamination at Camp Lejeune, the authors attempted to control for this by conducting a sensitivity analysis restricting the study population to those diagnosed with PD before January 13, 2017 (*i.e*., when the government ruling was published).

Exposure Assessment. Exposures were based solely on being stationed at Camp Lejeune or Camp Pendleton during a period of known water contamination; no chemical-specific exposures were estimated. Goldman *et al*. (2023) noted that they "cannot be certain that everyone who resided at Camp Lejeune between 1975 and 1985 was in fact exposed to biologically meaningful levels of contaminants," and that they were "unable to account for other environmental exposures that individuals from either camp may have sustained before, during, or after military service."

Outcome Assessment. Cases were identified using reliable and likely complete records from the VHA and Medicare. This study also focused on PD incidence, which is more informative than analyses evaluating mortality, because PD is not a fatal disease. Sensitivity analyses considering only those with probable PD as cases (*i.e*., excluding possible PD and other parkinsonism) were stronger because they were less likely

to include individuals who had parkinsonism symptoms but not PD as cases. Analyses considering prodromal symptoms are not specific to PD.

Covariates Considered. The authors controlled for age, sex, and smoking status (*i.e.*, ever and never). They did not consider or control for genetic factors, family history of PD, alcohol intake, or other possible chemical exposures, which could have resulted in uncontrolled confounding bias. Smoking status was also missing for about > 25% of participants.

Temporality. Being stationed on base was documented prior to diagnoses and the authors appropriately considered latency (*i.e.*, ≥ 12 years) between exposure and outcome.

5.3.3 Conclusion

Goldman *et al*. (2023) observed a statistically significant increased risk of PD among Camp Lejeune Marines and Navy personnel when compared with Marines and Navy personnel at Camp Pendleton. However, in a sensitivity analysis conducted to address potential selection bias by including only those whose PD was diagnosed prior to January 13, 2017 (the date of the government ruling on the presumptive service-connection for eight diseases associated with the contaminated water), there was no statistically significant association, indicating observed associations were likely due to selection bias. Importantly, the authors did not evaluate chemical-specific exposures; they only investigated PD risk associated with being stationed at Camp Lejeune. The authors also failed to consider all relevant covariates, which likely resulted in uncontrolled confounding, and a large portion of the population was excluded for not receiving VHA or Medicare health services. Overall, this study does not provide sufficient evidence for a causal relationship between TCE, PCE, benzene, or vinyl chloride exposure at Camp Lejeune and PD incidence.

5.4 Bove *et al*. (2024a)

5.4.1 Overview

Bove *et al*. (2024a) retrospectively evaluated PD mortality among 217,988 Marines and Navy personnel stationed at Camp Lejeune between 1975 and 1985 and 7,332 civilians employed at Camp Lejeune between October 1972 and December 1985. For comparison, the authors established a cohort of 232,026 Marines and Navy personnel and 6,677 civilian workers who met the same criteria at Camp Pendleton. Cohorts were constructed based on DMDC quarterly personnel data, which did not include military unit codes necessary to determine base locations until 1975. Since some Marines/Navy personnel who began active duty before 1975 could have been stationed at Camp Pendleton between 1975 and 1985, a subgroup of the full cohort was identified consisting of Marines and Navy personnel who began active duty between 1975 and 1985. This subgroup consisted of 159,128 and 168,406 Marines and Navy personnel at Camp Lejeune and Camp Pendleton, respectively. All participants were followed from January 1, 1979, to December 31, 2018.

According to Bove *et al*. (2024a), Camp Pendleton Marines and Navy personnel were selected as a reference cohort because they were reportedly unexposed to drinking water contaminated with industrial solvents and were similar to Camp Lejeune cohorts with respect to various demographic and behavioral factors. Exposure to TCE, PCE, benzene, and vinyl chloride at Camp Lejeune was not directly estimated for the purposes of this study. Instead, the authors compared Camp Lejeune and Camp Pendleton participants based on any assignment/employment and tertiles of duration of assignment/employment. To obtain vital status information, the investigators relied on data from a locator firm and the SSA Data for Epidemiological Researchers, which matched 99% of the records. Data on individuals who died or had

unknown vital status were submitted to the NDI to ascertain underlying and contributing causes of death. About 1% had unknown vital status after NDI linkage and were lost to follow-up but contributed person-years until the last date known to be alive.

Bove *et al*. (2024a) estimated SMRs and RRs. SMR calculations relied on age-, sex-, race-, and calendar-period-specific US mortality rates, while Poisson regressions compared sex-, race-, and 5-year age-specific PD deaths for Camp Lejeune *vs.* Camp Pendleton. HRs were also calculated using Cox extended proportional hazards regression, with age as the time variable and base location as time varying. Adjusted models included sex, race, education level, and rank (Marines & Navy personnel) or blue-collar work (civilian workers). No lag was implemented because > 75% of deaths occurred > 10 years after contamination ended at Camp Lejeune.

Between 1979 and 2018, Bove *et al*. (2024a) observed 15 PD deaths among Marines and Navy personnel at Camp Lejeune who began active duty between 1975 and 1985 and 64 PD deaths among all Marines and Navy personnel stationed between 1975 and 1985 at Camp Lejeune. These death counts were not statistically significantly different from expected based on PD mortality rates in the US general population (sub-group SMR = 1.47, 95% CI: 0.73-2.21; all personnel SMR = 1.01, 95% CI: 0.76-1.26) and they were also similar to counts observed for Camp Pendleton, in both Poisson regression (sub-group RR = 2.00, 95% CI: 0.86-4.87; all personnel RR = 1.06, 95% CI: 0.75-1.49) and Cox proportional hazards regression analyses (sub-group HR = 2.05, 95% CI: 0.86-4.87; all personnel HR = 1.29, 95% CI: 0.92-1.82). In analyses considering duration of assignment among those who began active duty between 1975 to 1985, all analyses were statistically null (HR range = 1.59-2.63), the lowest HRs were reported for those with the highest duration of assignment (> 7 quarter years).

For civilian workers, Bove *et al*. (2024a) observed 30 PD deaths. When compared to US mortality rates, there was no statistically significant difference in PD mortality at Camp Lejeune (SMR = 1.34, 95% CI: 0.86-1.82). In analyses based on Poisson regression and Cox proportional hazards regression, no associations were observed (RR = 1.15, 95% CI: 0.68-1.93; HR = 1.21, 95% CI: 0.72-2.04). Analyses considering duration of employment also did not yield any associations (HR range = 0.23-1.60).

Bove *et al*. (2024a) conducted quantitative bias analyses of non-differential exposure misclassification and unmeasured confounding from smoking, though they claimed changes were minor and may be canceled out by other confounders. The authors also ran analyses based on contributing causes.

5.4.2 Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 1%), and used appropriate comparison groups.

Exposure Assessment. The authors did not assess TCE, PCE, benzene, and vinyl chloride exposure. Instead, the authors relied on any assignment or employment at Camp Lejeune and Camp Pendleton and duration of assignment or employment. Although duration was meant to serve as a proxy for cumulative drinking water exposure, these results cannot be attributed to any specific chemical exposures that may have occurred at Camp Lejeune. Individual-level exposure information (*e.g.*, water consumption/exposure data) is necessary to make accurate chemical-specific risk estimations.

In addition, the authors conducted analyses of non-differential exposure misclassification, however, this misclassification was assumed to only decrease risk estimates.

Outcome Assessment. All cases were identified and validated using reliable sources (*i.e*., SSA Data for Epidemiological Researchers and NDI). After accounting for those lost to follow-up, there were no missing data with regard to outcome assessment. However, the authors only evaluated mortality, which is a serious limitation, as PD is not a fatal disease.

Covariates Considered. Bove *et al*. (2024a) controlled for important covariates such as age, sex, race, and (for civilians) potential occupational exposures through their incorporation of the blue *vs*. white-collar work category. Other relevant covariates, such as family history of PD, heavy alcohol intake, and genetic factors, were not considered or controlled for, which may have resulted in some confounding bias. Race data were also missing for about 5.2 and 14.7% of Camp Lejeune and Camp Pendleton Marines and Navy subgroup personnel and civilian workers, respectively.

The authors also considered smoking in quantitative bias analyses. The quantitative bias analyses, however, were based on results from smoking-related "negative control diseases" (*i.e*., mortality due to chronic obstructive pulmonary disease [COPD], because the HR was higher than for cardiovascular disease) to estimate prevalence differences in smoking between Camp Lejeune and Camp Pendleton. Since these bias estimates were based on a series of assumptions that were not validated (*i.e*., true risk of PD mortality due to smoking; the prevalence of smoking in Camp Lejeune and Camp Pendleton; a uniform distribution of smoking among the populations), the results were uninterpretable.

Temporality. DMDC quarterly personnel data that were used for exposure assessment were documented prior to PD mortality. In addition, although the study does not consider any latency period between exposure and outcome, the authors do mention that 75% of deaths occurred > 10 years after water contamination ended. In addition, for civilian workers, there is a category of duration of employment that is based on greater than or equal to 5.75 years of employment, which would allow for appropriate exposure-response latency.

5.4.3 Conclusion

Bove *et al*. (2024a) did not observe any associations between any assignment or employment at Camp Lejeune or duration of assignment or employment at Camp Lejeune and PD mortality. There were also numerous study quality concerns that impact the interpretation of the study results, most notably, the lack of any chemical-specific risk assessments and the reliance on duration of assignment or employment analyses as a proxy for chemical-specific exposure assessments. Without direct exposure assessments for TCE, PCE, benzene, or vinyl chloride, it is impossible to attribute PD mortality risk to any specific chemical. In addition, the authors were not able to control for or consider some relevant confounders, and their quantitative bias analysis to assess confounding from smoking on PD mortality was flawed. Therefore, this study does not provide sufficient evidence for a relationship between TCE, PCE, benzene, or vinyl chloride exposure and PD mortality.

5.5 Toxicology

No animal carcinogenicity or mechanistic studies have investigated exposures to Camp Lejeune drinking water. As discussed in the following sections, toxicity studies of TCE, PCE, and vinyl chloride do not support a causal association with PD.

5.6 Exposure

Bove *et al*. (2014a) and ATSDR (2018b) estimated exposures to TCE, PCE, benzene, and vinyl chloride in Camp Lejeune drinking water 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.

Dr. Hennet's and Dr. 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.

As noted above, 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."

5.7 Conclusions

Three studies evaluated PD risks among Marines or Navy personnel stationed at Camp Lejeune and three studies evaluated PD risks among 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 PD. Most risk estimates were small and statistically null, and the few statistically significant risk estimates had wide CIs and were not reported across other analyses of the Camp Lejeune population, indicating a high likelihood of bias or confounding, such that they do not provide evidence of a causal link between exposure to contaminated water at Camp Lejeune and PD. These studies all had several methodological limitations, including a high likelihood of exposure misclassification, a lack of adjustment for relevant covariates like alcohol use, and a potential for selection bias. There are no toxicity or mechanic studies of Camp Lejeune drinking water, but toxicity and mechanistic studies do not provide evidence that exposures to TCE, PCE, or vinyl chloride can cause PD.

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

6 TCE and PD

TCE is a colorless, nonflammable, and volatile liquid (ATSDR, 2019a; US EPA, 2020a). While there are a few instances in which TCE occurs 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 (ATSDR, 2019a; IARC, 2014a; US EPA, 2020a). TCE has also been used by the textile processing and dry-cleaning industries (ATSDR, 2019a; IARC, 2014a). Impurities of commercially manufactured TCE include both PCE and 1,1,1-TCA (IARC, 2014a).

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 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 (ATSDR, 2019a). 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.

Few epidemiology studies have evaluated associations between TCE exposure and PD. These studies have mixed results and several methodological limitations and, as such, do not provide evidence for an association. There is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD. While subchronic- and subacute-duration experimental animal studies have reported some PD-associated pathological or behavioral effects in rats and mice dosed with TCE, the exposure conditions were much higher than human exposures, and still the magnitudes of the effects (specifically on dopaminergic neuron loss and reduced dopamine levels in the SNpc) were below those necessary to produce clinical signs of PD in humans.[10] Furthermore, there is no clear mechanism by which TCE may affect the dopaminergic system in humans. No scientific or regulatory agency has concluded that TCE exposure is a cause of PD. The scientific evidence regarding TCE exposure and PD is discussed below.

6.1 Epidemiology

I reviewed the studies considered by US EPA (2011a, 2020a) and ATSDR (2017a, 2019a), and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). I identified four cohort and three case-control studies in six unique populations that examined the association between TCE exposure and PD, and a few case studies and case series. I review here all Camp Lejeune studies that evaluated TCE exposures, even if overlapping, for completeness. I do not discuss Camp Lejeune studies in this section if they did not discuss TCE-specific exposures (*e.g.*, exposure was assumed if a person was stationed at Camp Lejeune). All of the epidemiology studies included individuals who were potentially exposed to both TCE and PCE, as well as other chemicals, from drinking water, hobbies, or at the workplace, so it was not possible to tease out associations

[10] As discussed in Section 4, some estimates of the magnitude of loss of dopaminergic neurons in the SNpc required to produce clinical signs of PD in humans are as low as 30-50%, but most estimates are at least 50%, and generally range from 60% to 80% (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024).

for either chemical alone. Most of the risk estimates reported in these studies were identical for TCE and PCE, and not specific to either chemical.

I summarize the characteristics, results, and quality of the epidemiology studies related to TCE exposure and PD below and in Attachment D, Tables D.1-D.4, and in Attachment C, Table C.1. Overall, primarily because of their methodological limitations, these studies do not provide evidence for an association between TCE exposure and PD.

6.1.1 Cohort Studies

I identified four cohort studies that evaluated the relationship between TCE exposure and PD, all of which were conducted in the US (Attachment D, Tables D.1 and D.2).[11] Two of these studies examined this relationship among civilian or US Marines and Navy personnel at Camp Lejeune potentially exposed to TCE *via* contaminated water and included overlapping populations (mortality: Bove *et al*. [2014a]; incidence: ATSDR [2018b]). I discuss these studies in detail in Section 5. The other cohort studies evaluated PD mortality risk among microelectronics and business machine facility employees occupationally exposed to TCE (Silver *et al*., 2014) and among partners at a law firm located across from a large dry cleaner in Rochester, New York (Dorsey *et al*., 2024).

None of the cohort studies assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Table C.1). In the Camp Lejeune studies, exposure was based on the estimated monthly average TCE concentration in groundwater while participants lived or worked on base. There was no information on water consumption or actual individual exposures to TCE or other chemicals in drinking water, including PCE. Silver *et al*. (2014) only reported results for the entire population of participants who worked at the microelectronics and business machine facility; they did not report any risk estimates for TCE exposure and PD. Dorsey *et al*. (2024) considered partners exposed if they had been employed at the law firm for over 1 year. Additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between TCE exposure and PD.

Bove *et al*. (2014a)

Overview

Bove *et al*. (2014a) retrospectively evaluated PD deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985, and who had been potentially exposed to TCE-contaminated drinking water on base. Between 1979 and 2008, there were five PD deaths in the cohort. There was no statistically significant association between PD mortality and > median cumulative TCE exposures compared to < median cumulative TCE exposures (HR = 2.51, 95% CI: 0.21-30.76). The authors reported similar results in models of $\log_{10}$ continuous cumulative TCE exposure.

Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 2%), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the

[11] In addition to these five studies, Bove *et al*. (2014b) evaluated health risks in 154,932 Marines and Navy personnel stationed at Camp Lejeune during the time of the water contamination, using similar methods to those used in Bove *et al.* (2014a). There were fewer than five PD deaths observed, so they did not report the results of analyses of TCE exposure and PD.

study, less than 15% of the study population had died, and only a small number of PD deaths were observed (n = 5), which limits precision of the estimated associations.

Exposure Assessment. Potential exposures were estimated based on groundwater fate and transport models of the monthly average concentrations of TCE in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. These direct measurements are more reliable than exposure estimates that are not based on any quantitative information, but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely.

Outcome Assessment. The study assessed PD mortality, which is weaker than examining PD incidence, because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e.*, SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for sex and occupation (blue *vs.* white collar). The authors considered but did not control for age because the adjusted results differed from the unadjusted results by less than 10%. The authors did not consider or control for genetic factors, family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly to use as a proxy for other potential occupational exposures, it is unclear if they analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

Silver *et al*. (2014)

Overview

Silver *et al*. (2014) identified 43 PD deaths among 34,494 employees of a microelectronics and business machine facility, where TCE was used for pin degreasing and circuit board processing between 1969 and 2009. The authors reported no statistically significant increased risk of PD deaths among male hourly (SMR = 0.87, 95% CI: 0.54-1.34), male salaried (SMR = 1.21, 95% CI: 0.73-1.89), female hourly (SMR = 0.73, 95% CI: 0.15-2.14), or female salaried (SMR = 0.00, 95% CI: 0.00-21.8) employees.

Quality Considerations

Study Population. The study used appropriate comparison groups, and likely had low attrition because follow-up for PD deaths after employment used reliable government records (SSA, NDI, and Internal Revenue Service [IRS]). This cohort was relatively young (mean age at hire was in the mid-20s and average

duration of follow-up was approximately 26 years), so only a small number of deaths had occurred by the end of the follow-up, limiting the precision of the estimated effect estimates.

Exposure Assessment. Exposure characterization was based solely on employment at the facility without consideration of actual exposures or exposure intensity. The exposure assessment was further limited by missing and sparse data during the periods of highest TCE use at the facility, likely resulting in misclassification.

Outcome Assessment. As noted above, the study used reliable government records (SSA, NDI, and IRS) to identify deaths, but PD mortality is not a good surrogate for PD incidence because PD is not a fatal disease.

Covariates Considered. The authors controlled for age and sex, but did not consider or control for genetic factors, family history of PD, heavy alcohol intake, or smoking, which could have resulted in uncontrolled confounding. The authors only considered covariates at a single time point and the amount of missing covariate data was not reported, which further limits the ability to fully interpret the results.

Temporality. Occupational histories were collected separately from outcome data and the appropriate windows of exposure (*e.g.*, 10-year lag) were considered.

ATSDR (2018b)

Overview

In an overlapping population of that analyzed by Bove *et al*. (2014a), ATSDR (2018b) conducted a health survey from 2011 to 2012 that collected information on PD and lifestyle and demographic factors from 50,684 Marines and Navy personnel and 2,168 civilian employees stationed or employed at Camp Lejeune between 1972 and 1985. The authors assessed PD incidence and levels of exposure to TCE. The authors reported no association between any level of cumulative exposure (low exposure [< 110 µg/L-months] OR = 0.86, 95% CI: 0.47-1.59; medium exposure [110 - < 11,030 µg/L-months] OR = 0.87, 95% CI: 0.46-1.62; high exposure [≥ 11,030 µg/L-months] OR = 0.29, 95% CI: 0.87-8.94) in Marines and Navy personnel at Camp Lejeune compared to those at Camp Pendelton. When they compared Marines and Navy personnel with medium or high exposure at Camp Lejeune to those with low exposure, results were similar to those reported for comparisons to Marines and Navy personnel at Camp Pendleton. The authors reported an association between PD and medium levels of cumulative exposure (10,868 - < 50,563 µg/L-months, OR = 3.47, 95% CI: 1.18-10.22), but not for low (< 10,868 µg/L-months, OR = 2.78, 95% CI: 0.87-8.94) or high levels (≥ 50,563 µg/L-months, OR = 2.86, 95% CI: 0.67-12.13) in civilians employed at Camp Lejeune. There were no associations between medium or high levels of exposure compared to low exposures in civilians at Camp Lejeune.

Quality Considerations

Study Population. This study used appropriate comparison groups, but selection bias is likely. 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 authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

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

Exposure Assessment. Exposures to TCE were estimated based on groundwater fate and transport and water distribution system models coupled with historical occupation codes, period and duration of employment or residence, and workplace or residence location. These TCE-specific estimates are more reliable than exposure estimates that are not based on any quantitative information (*e.g.*, assignment on base), but without a direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption/exposure data), it is still likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures 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 exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Finally, there was a high correlation between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs in the ATSDR (2018b) study, which limits the interpretation of chemical-specific results.

In a deposition, Dr. Bove (2024a) states, "The Marine Corps…didn't know, where barracks were on base, where units were barracked on base. And we relied on CAP [community assistance panel] members plus people they knew who had that memory…" Dr. Bove (2024a) also stated that they were not able to take into account a Marine's deployment off base and so they assumed that the DMDC data represented a continuous presence at Camp Lejeune, raising more concerns over 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al.*, 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al.*, 1991) or multiple exposure categories (Dosemeci *et al.*,

1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed that nondifferential exposure measurement error could lead to bias towards or away from the null in a recent deposition, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

Outcome Assessment. Cases were confirmed using medical records or death certificates, but initial reliance on self-reported cases could have resulted in some missed cases. There were a small number of PD cases in the civilian population (n = 20), which may have resulted in risk estimates with reduced precision. This analysis also focused on PD incidence, which is more informative than analyses evaluating mortality, since PD is not a fatal disease.

Covariates Considered. The authors only controlled for sex in their analyses. They considered but did not control for age, smoking, alcohol, or other potential occupational exposures or chemical exposures because adjusted results differed from unadjusted results by less than 10%. The authors did not consider or control for genetic factors or family history of PD. Covariate data were collected at a single timepoint *via* self-report and smoking, alcohol consumption, and other occupational exposures were missing for more than 5% of participants, increasing the likelihood of biased results.

Temporality. The study exposure and outcome periods overlapped, with follow-up beginning coincident with first exposure (*i.e.,* exposures could continue to occur after follow-up began). Some participants were followed for up to 40 years, but the authors did not consider a latency period.

Dorsey *et al*. (2024)

Overview

Dorsey *et al*. (2024) retrospectively evaluated PD among 79 partners at a law firm in an office tower (*i.e*., the tower cohort) across from a large dry-cleaner in Rochester, New York. The dry-cleaner operated between 1950 and 1994, and in 1992, TCE, PCE, and other chemicals[12] were found in the surrounding soil. The flow of groundwater was determined to be from the dry-cleaner toward the office tower in which the law firm operated, potentially exposing the building occupants. Partners included in the study were employed at the firm for ≥ 1 year between 1968 and 2001. Dorsey *et al*. (2024) identified four cases of PD (5.1%) in the tower cohort through March 2023. The cumulative incidence (referred to as prevalence in this study) of PD in the tower cohort was statistically significantly greater than what would be expected based on rates in the general population (1.7%) (p = 0.01), but not greater than what was observed in a comparison group of attorneys (1.3%) recruited from the local bar association's newsletter, flyers, and word of mouth (p = 0.21).

Quality Considerations

Study Population. The study did not use appropriate comparison groups. The characteristics of the tower cohort and the two comparison groups were very different. The tower cohort was comprised solely of partners in a law firm (*i.e*., highly educated), were 89.9% male, 97.3% white, 20.8% veterans, and 50% retired. These factors were not similar (except for educational attainment) compared to the comparison

[12] Dorsey *et al*. (2024) reported that other chemicals at the site "included methylene chloride, chloroform, chlorobenzene, 1,4-dichlorobenzene, 1,1,2,2-tetrachloroethane, cis 1,2-dichloroethene, 1,3,5- and 1,2,4–trimethylbenzene, isopropylbenzene, n-propylbenzene, sec-, and tert-butylbenzene, acetone, ethylbenzene, isopropylbenzene, naphthalene, toluene, p-isopropyltoluene, m-o-and p-xylene, and Stoddard solvent." These chemicals were not measured in the groundwater "because the groundwater at the site was not used for drinking" (Dorsey *et al*., 2024).

group and were likely very different from the characteristics of the general population. Participants in the tower cohort could be dead or alive, while participants in the comparison group were alive. Participation rates also varied, with the tower cohort having a participation rate of 96.3%, while only 63% of attorneys in the comparison group were eligible and participated. It is not known how those who did not participate differed from those who did.

Exposure Assessment. Because employment at the law firm for over 1 year was the only criterion for being considered to have been exposed to TCE or PCE, there were no missing data on exposure. However, there was no consideration of individual-level exposures. Dorsey *et al*. (2024) did not report when the contamination started, only that the dry-cleaner operated from 1950 to 1994, and that an environmental assessment found contaminated soil around the dry-cleaner in 1992. There was a parking garage underneath the tower, and it was reported that "TCE, PCE, or other chemicals were still found in the exhaust gas from the garage ventilation system until the system was shut down in 2003" (Dorsey *et al*., 2024). There was no information on whether there was any potential exposure outside of the garage, how long the garage had been contaminated, or who in the tower cohort used the garage, how frequently, or what the chemical concentrations were in the garage over time.

Outcome Assessment. The study assessed cumulative incidence of PD (referred to as prevalence in the study), but deceased cases were included in the tower cohort, but all participants in the comparison group were alive at the time of the study, potentially biasing results. Cases were initially self-reported but confirmed using medical records and clinical assessments of PD, such as the Gelb Criteria for the Diagnosis of Parkinson's Disease.

Covariates Considered. The authors controlled for age in both comparisons, and sex in the comparison to the general population, but did not control for other key covariates including race/ethnicity, smoking, heavy alcohol intake, or genetic factors. They also did not control for other possible chemical exposures, despite describing other chemicals at the dry-cleaning facility. They also did not control for family history of PD despite 16% of participants in the tower and comparison group reporting a family history of PD. It is not clear if any of the cases in the tower cohort had a family history of PD and they did not control for this factor in their analysis. The amount of missing covariate data was not reported, which further limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from disease status data, but there was an insufficient consideration of latency (*i.e*., ≥ 1 year of employment at tower).

6.1.2 Case-Control Studies

I identified three case-control studies examining the relationship between TCE exposure and PD incidence (Attachment D, Tables D.3 and D.4). Two of these studies examined this relationship in overlapping Finnish general population samples using occupational data reported on censuses that were linked to the Finnish Job Exposure Matrix (FINJEM) to estimate probabilities of chemical exposures. Similar to the cohort studies on TCE and PD, none of the case-control studies assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Attachment C, Table C.1). Study summaries and additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between TCE exposure and PD.

Goldman *et al*. (2012)

Overview

Goldman *et al*. (2012) examined risk of PD in 99 discordant male twin pairs from the National Academy of Sciences (NAS)/NRC World War II Veteran Twins Cohort study. They reported an association between PD and any TCE exposure (OR = 6.1, 95% CI: 1.2-33) and an increased risk of PD associated with an increase of one tertile of TCE exposure years (OR = 3.2, 95% CI: 1.1-10), and with an increase of one tertile of the cumulative exposure index (defined as the product of exposure intensity, hours exposed per year, and years exposed, summed across all jobs and hobbies) (OR = 5.2, 95% CI: 1.03-26). In a recent interview, Dr. Goldman (2023) noted that in addition to a few case reports, they "only had 10 or 12 exposed individuals. So it was suggestive, the epidemiology, but the numbers and the power is really limited."

Quality Considerations

Study Population. This discordant twin study appropriately selected and compared participants, however, the results may not be generalizable to the general population. There was a high non-response rate (60-63%) in both cases and controls, and it is unknown how those who participated differed from those who did not. The overall sample size (99 pairs) and proportion of exposed participants (3-10%) were small, which is reflected in the low precision of the effect estimates.

Exposure Assessment. There was likely substantial exposure misclassification because of the indirect measurement of exposure based on self- or proxy- reported job and hobby histories. While some analyses considered duration and cumulative exposure, others only assessed ever/never exposure. The proxy response rate was much greater for cases (46.5%) than controls (18.2%), which may have resulted in some information bias.

Outcome Assessment. All cases were likely captured, as this is a study of veterans, and cases were identified using Veterans Affairs, Health Care Financing Administration, NDI, and the NAS/NRC World War II Veteran Twins Cohort study records, and all were confirmed by a review of in-person evaluations, neurological exams, and medical records by two neurologists.

Covariates Considered. Because the participants were all male twins, age, sex, and race were the same among pairs. The authors controlled for respondent type (self or proxy) and smoking in the primary analysis, and certain solvent exposures (toluene, xylene, n-hexane, carbon tetrachloride [CCl_4], PCE) in secondary analyses. The authors did not consider or control for other solvent exposures or alcohol intake, which could have resulted in uncontrolled confounding. There were no missing covariate data, but variables were only considered at a single timepoint.

Temporality. There was an average of 38.3 years between first reported exposures and PD diagnosis. Information on exposures occurring decades prior was collected after the PD diagnoses, which could have resulted in recall or information bias. Only the sensitivity analyses considered latency (10-year lag).

Sallmén *et al.* (2023)

Overview

Sallmén *et al*. (2023) updated and expanded on a case-control study by Nielsen *et al*. (2021). This case nationwide Finnish case-control study included individuals who were between the 45 and 84 years of age between 1995 and 2014. The authors identified 17,187 incident PD and comparable movement disorder

cases using prescription reimbursements registered under the Social Insurance Institution of Finland. A total of 35,738 controls were selected using incidence density sampling from the Population Information System register and matched on sex, birth year, and residency in Finland on index date. The authors reported no association between PD and any level of TCE exposure (> 0-4.9 parts per million- [ppm-]years IRR = 0.95, 95% CI: 0.86-1.05; 5-14.9 ppm-years IRR = 0.97, 95% CI: 0.87-1.10; 15-225 ppm-years IRR = 1.03, 95% CI: 0.90-1.18). The authors also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to the chemical-specific methods) and probabilistic bias analyses (PBAs) that accounted for exposure measurement error. The results from the PBAs were attenuated, suggesting that the conventional analyses that did not account for exposure misclassification may have overestimated risks. PBAs were not run for TCE-specific exposures.

Quality Considerations

Study Population. The case and control groups were appropriate, but the authors excluded approximately half of the potential sample population due to missing or incomplete census or occupational data.

Exposure Assessment. The probability of exposure for individual cases and controls was estimated using FINJEM, which was linked to occupational information obtained from multiple national censuses (carried out every 5 years from 1970 to 2000 and annually from 2004 to 2008). Exposures may have been misclassified because they were based on job titles and no actual exposures were measured. The duration and intensity of exposures was considered but time variations in exposure (*e.g.*, daily or annually) were not considered. Only about 6-7% of participants were estimated to have any TCE exposure, which limited the precision of estimated effect estimates.

Outcome Assessment. The identification of cases through prescription reimbursements registered under the Social Insurance Institution of Finland is reliable and likely complete. The inclusion of comparable movement disorders limits the interpretation of the results, as grouping these outcomes with PD may be inappropriate if they have different underlying etiologies.

Covariates Considered. The authors adjusted for sex, birth year, and probability of smoking in primary analyses, and considered other chemical exposures (chromium, nickel, welding, polycyclic aromatic hydrocarbons, and aliphatic/alicyclic hydrocarbons or aromatic hydrocarbons) only in secondary analyses because the adjusted results differed by less than 10% from the unadjusted results. The authors did not control for or consider genetic factors or family history of PD or alcohol intake, which may have resulted in uncontrolled confounding. Covariates were only considered at a single time point and the smoking variable was estimated based on surveys of Finnish residents linked to occupation and sex, which could have resulted in additional confounding or bias.

Temporality. Occupational histories were documented prior to the outcomes and an appropriate consideration of latency was included (≥ 5 years between exposure and outcome).

6.1.3 Case Reports and Case Series

There have been a few case reports and case series in which individuals with PD or parkinsonism reported past TCE exposure (reviewed by Dorsey *et al*. [2023]). For example, Gash *et al*. (2008) conducted neurological and motor speed evaluations on 30 coworkers and reported that "three workers with workstations adjacent to the trichloroethylene source and subjected to chronic inhalation and dermal exposure from handling trichloroethylene-soaked metal parts had Parkinson's disease," while workers more distant from the source had many features of parkinsonism. The authors stated, "It is important to recognize that this study was not a large-scale epidemiological investigation designed to address recall, case finding,

or other sources of bias." Similarly, Dorsey *et al*. (2023) noted, "The evidence linking possible exposure to TCE in these cases is circumstantial." Because there are no individuals without PD for comparison, it is not possible to determine whether TCE was a causal factor in any individual in these case reports and case-series.

6.1.4 Conclusions

To date, only seven epidemiology studies in six unique populations have evaluated TCE exposure and PD, and risk estimates were not consistently strong or > 1, and the majority did not report statistically significant associations. All reported strong associations (*i.e*., risk estimates > 2), including the only positive statistically significant association, had wide confidence intervals. All of these studies have methodological limitations that impact the interpretation of their results. Most notably, no studies provided direct measurements of individual-level TCE exposures, as drinking water studies do not consider whether or what amount of water individuals drank, and hobbies, job categories, or place of employment used in other studies may not be reliable surrogates for individuals' exposures to TCE. Because of these methodological limitations, I conclude that currently available epidemiology evidence does not support a causal association between TCE exposure and PD.

6.2 Toxicology

I identified relevant toxicity studies by reviewing US EPA (2011a, 2020a) and ATSDR (2017a, 2019a), and by conducting literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). No chronic animal bioassays have examined PD-associated pathological or behavioral outcomes. Subchronic and subacute laboratory animal studies that evaluated pathological or behavioral outcomes associated with PD following TCE exposure are discussed below and summarized in Table 6.1 and Attachment E, Tables E.1-E.7.

Overall, these animal studies were higher quality with respect to reporting, confounding, and attrition, but lower quality with respect to allocation, chemical administration and characterization, and outcome sensitivity and specificity (Table 6.1 and Attachment E, Table E.6 and E.7). Only one of 12 total studies evaluated TCE inhalation and PD-associated pathological outcomes, but the relevance of the dose tested to humans is unclear, and the magnitude of dopaminergic neuron loss was below levels required to produce clinical signs of PD in humans. The other 11 studies involved oral or intraperitoneal (i.p.) injection exposure, and 10 of these studies evaluated only one dose per species, so they were unable to evaluate dose-response. Some of the tested doses were close to those causing unrelated toxic effects and even lethal effects in animals (ATSDR, 2019a). Doses tested in the oral and i.p. injection studies ranged from 200 to 1,000 mg/kg-day, which are orders of magnitude higher than typical human exposures (see, for example, Gash *et al*., 2008), including at Camp Lejeune.[13] I conclude that, as a whole, evidence from experimental animal studies does not support a causal relationship between TCE exposure and PD in humans.

[13] For example, the 1,000 mg/kg-day TCE dose evaluated by Gash *et al*. (2008) in Fischer 344 rats was estimated to be equivalent to 53-56 mg/kg-day in humans based on the total amount of TCE metabolized per unit adjusted body weight as the dose metric, or 192-571 mg/kg-day based on the area under the curve of venous blood concentration of TCE as the dose metric, using US EPA's physiologically based pharmacokinetic (PBPK) model for TCE (US EPA, 2011). In contrast, the highest adult intakes of TCE from exposures to TCE in drinking water at Camp Lejeune were estimated to be lower than 0.2 mg/kg-day (NRC, 2009).

Table 6.1 Animal Studies of Trichloroethylene and PD

Study	Study Design			PD Outcomes Evaluated[a,b]								
	Animal	Doses	Duration (Weeks)	A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Subchronic – Inhalation												
Adamson *et al.* (2023)	Lewis rats	0, 50 ppm	8		—	—		—		—	—	
	C57BL/6J mice	0, 100 ppm	12	—	—	—		—		—	—	
Subchronic – Oral Gavage												
Gash *et al.* (2008)	Fischer 344 rats	0, 1,000 mg/kg-d	6	NR				—	—	—		—
Liu *et al.* (2010)[c,d]	Fischer 344 rats	0, 250, 500, 1,000 mg/kg-d	6	NR				—	—	—		
Liu *et al.* (2018)	C57BL/6 mice	0, 400 mg/kg-d	13 or 35					NS	—	—		
De Miranda *et al.* (2021)[e]	Lewis rats	0, 200 mg/kg-d	1-6		—	—		—		—	—	
Ilieva *et al.* (2022)	Lewis rat	0, 200 mg/kg-d	6	–	–	–	–	–	–	–	–	–
Ilieva *et al.* (2024)	Lewis rat	0, 200 mg/kg-d	3-6	–	–	–		–	–	–		–
Srivastava *et al.* (2024)[f]	Wistar rat	0, 1,000 mg/kg-d	8	–	–	–	NR	–	–	–	–	
Subchronic – Intraperitoneal Injection												
Keane *et al.* (2019)	C57BL/6 mice	0, 1,000 mg/kg-d	8	—	—	—		—	—	—	—	NS
Subacute – Oral Gavage												
Sauerbeck *et al.* (2012)	Fischer 344 rats	0, 1,000 mg/kg-d	1 or 2	—	—	—	NS	NS	—	NS	NS	NS
Subacute – Intraperitoneal Injection												
Guehl *et al.* (1999)	OF1 mice	0, 400 mg/kg-d	4	—	—	—		—	—	—	—	NS
Otsuki *et al.* (2016)	C57BL/6 mice	0, 500 mg/kg-d	4	—	NS	NS	NS	—	—	—	—	

Notes:

A = α-Synuclein Levels in SNpc; D = Dopamine Levels in SNpc; Dm = Dopamine Metabolite Levels in SNpc; Dn = Dopamine Neuron Levels in SNpc; Dr = Dopamine Receptor Levels in SNpc; Dtrm = Dopamine Neuron Terminals; Dtrp = Dopamine Transporter Levels in SNpc; Mi = Mitochondrial Function in SNpc; Mo = Motor Function; NR = Statistical Significance Was Not Reported; NS = Not Statistically Significant; PD = Parkinson's Disease; SNpc = Substantia Pars Compacta; TCE = Trichloroethylene.

(a) Cells shaded in light gray denote the outcome was statistically significant under at least one exposure condition.

(b) Dashes denote the outcome was not examined.

(c) Liu *et al.* (2010) reported statistically significant losses of dopaminergic neurons at 500 and 1,000 mg/kg-d, but not 250 mg/kg-d TCE.

(d) Liu *et al.* (2010) measured dopaminergic neuron numbers following exposure to 0, 250, 500, or 1,000 mg/kg-d TCE, but they conducted all other experiments with the 1,000 mg/kg-d dose only.

(e) Data shown are from Cohorts 1 and 2 of De Miranda *et al.* (2021). Data from Cohort 3 for which LRRK2 activation was evaluated are not shown because the authors concluded that the mechanism by which TCE may activate LRRK2, and the extent that LRRK2 activation by chemicals may affect the dopaminergic system of humans carrying LRRK2 mutations, "is unclear" (De Miranda et al., 2021). Briefly, in Cohort 3, male Lewis rats were exposed to 0, 50, 100, 200, 400, or 800 mg/kg-day TCE for 3 weeks. Increased markers of LRRK2 activation were only associated with exposure to doses ≥ 200 mg/kg-day.

(f) Srivastava *et al.* (2024) treated rats with 1,000 mg/kg-d TCE and PD therapeutic compounds (Levodopa + Carbidopa) or an antioxidant compound (ALP-SENF).

6.2.1 Subchronic Studies

I identified 10 subchronic TCE bioassays that evaluated pathological outcomes associated with PD in rodents (seven in rats and three in mice) (Table 6.1 and Attachment E, Tables E.1-E.3). In two of these bioassays, animals were exposed to TCE *via* inhalation, and in the other eight bioassays, they were exposed orally or *via* i.p. injection.

Inhalation

6.2.1.1 Adamson *et al*. (2023)

Only two inhalation bioassays have evaluated TCE exposure and PD. Adamson *et al*. (2023) exposed male and female Lewis rats to 0 or 50 ppm TCE, 7 hours/day for 8 weeks. In addition, male and female C57BL/6J mice were exposed to 0 or 100 ppm TCE, 7 hours/day for 12 weeks. Adamson *et al*. (2023) reported that TCE treatment was associated with statistically significant aggregation of α-synuclein (in rats only, α-synuclein levels were not examined in mice), decreased dopaminergic neuron numbers (stated to be "approximately" 50 and 30% reduction in rats and mice, respectively), and decreased dopaminergic neuron terminals in the SNpc, as well as alterations in motor function measures in rats and mice. With respect to the motor function measures, Adamson *et al*. (2023) reported inconsistent effects on gait parameters in TCE-exposed rodents; that is, some gait measures increased, some gait measures decreased, and some were unaffected. Regarding the loss of dopaminergic neurons, the magnitude of loss was less than that required to produce clinical signs of PD in humans (60-80%) (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). Further, Adamson *et al*. (2023) did not measure dopamine content in SNpc, so it is unclear whether dopamine levels may have been maintained by the surviving neurons. Mitochondrial function in the SNpc was not assessed in this study.

Adamson *et al*. (2023) stated, "[T]o our knowledge, [these are] the first data on parkinsonian neurodegeneration or associated pathology from passive, chronic TCE inhalation," but this study should not be characterized as "chronic." Adamson *et al*. (2023) concluded, "Our data here suggest that TCE inhalation causes potent dopaminergic neurotoxicity at much lower doses than previously examined,"[14,15] and that "despite a lower dose, 50 ppm TCE inhalation caused more dopaminergic neurodegeneration than 200 mg/kg TCE *via* oral ingestion," as observed in a previous study in their laboratory (De Miranda *et al*., 2021).

Adamson *et al*. (2023) estimated the human equivalent dose in this study using the following equation:

$$\text{HED (mg/kg)} = \text{animal dose (mg/kg)}/\text{animal correction factor}$$

The authors state, "Rat and mouse correction factors (6.2 and 12.3, respectively) were obtained from Nair and Jacob (2016) to scale body surface area for a 60 kg human." This equation is for comparing oral exposures, not inhalation exposures. Humans actually have a lower air intake per kg than rodents, so our intake is lower at any given air concentration (Rhomberg, 2009). Ultimately, to scale rodent inhalation exposures to humans, the timing of exposure is a critical factor. For example, in this study, rats and mice

[14] Adamson *et al*. (2023) stated, "Based off the equation below by Nair and Jacob (2016), HED [human equivalent dose] for 50 ppm in rats and 100 ppm in mice was determined to be approximately equivalent to 8 ppm in a human."

[15] Using route-to-route conversion, I estimate that the 8 ppm TCE is approximately equal to 7.2 mg/kg-day. First, 8 ppm TCE is approximately equivalent to 43 mg/m^3, based on the molecular weight of TCE of 131.4 g/mol (8 ppm x 131.4 / 24.45 = 43 mg/m^3) (NIOSH, 2003). Accordingly, 43 mg/m^3 TCE is approximately equivalent to 7.2 mg/kg-day, based on an occupational inhalation rate of 10 m^3/day and a body weight of 60 kg (43 mg/m^3 x 10 m^3/day / 60 kg = 7.2 mg/kg-day).

were exposed for 7 hours a day for 8 weeks and 12 weeks, respectively. One would need only to determine how many hours a day a human was exposed to scale the concentration.

With respect to species differences, owing to fundamental differences in physiology and anatomy, laboratory animals such as rodents have substantially greater effects from exposures to chemicals *via* inhalation relative to humans. According to Illum (2000), "It is important to consider, when interpreting results obtained in animals, that the olfactory region, of, for example, the rat and other commonly used animal models, is covering a large part of the nasal mucosa, whereas in humans the olfactory epithelium covers only a small area in the roof of the nasal cavity. Hence, it is most likely that the olfactory transport of drugs will be much more pronounced in rats than for the same compounds in humans." The statements pertained to pharmaceuticals, but the principles can be applied to chemicals generally, including TCE.

In fact, as noted by NRC (2009) in its report, "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects," "for equivalent inhalation exposures to TCE and other VOCs, internal doses are substantially higher in rodents than in humans" (Bruckner *et al*., 2008). NRC (2009) further stated, "Mice and rats absorb more inhaled TCE and PCE, metabolically activate more of their absorbed dose, and inactivate epoxide metabolites less efficiently than do humans." Since rodents have substantially greater effects from exposures to chemicals *via* inhalation relative to humans, thus caution is warranted with respect to interpreting any potential relevance to humans (NRC, 2009).

In summary, Adamson *et al*. (2023) is the only study conducted that evaluated TCE inhalation and PD-associated pathological outcomes, it used only one very high dose in rats and mice, the reported effects on motor function were inconsistent, and the magnitude of dopaminergic neuron loss was below levels required to produce clinical signs of PD in humans. Thus, this study does not provide evidence that human inhalation exposures to TCE can cause PD.

Oral

6.2.1.2 Gash *et al*. (2008)

Gash *et al*. (2008) exposed male Fischer 344 rats to 0 or 1,000 mg/kg-day TCE for 6 weeks *via* oral gavage. PD-associated pathological outcomes were examined in the SNpc and striatum, two brain regions in the nigrostriatal dopamine system and involved in the progression of PD. Potential PD-associated behavioral effects of TCE (*i.e*., motor function) were not examined in this study.

In the SNpc, exposure to TCE was associated with a statistically significant 45% loss of dopaminergic neurons, decreased mitochondrial complex I activity, a 20% decrease of dopamine levels, a decrease in dopamine metabolites (% not stated), and accumulation of α-synuclein. By contrast, in the striatum, there was statistically significant decreased dopamine metabolism, but an increase in mitochondrial complex I activity (noted to be a potential compensatory response) and no effect on dopamine levels.

The authors concluded TCE "joins other mitochondrial neurotoxins, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and some pesticides, as a risk factor for parkinsonism," and that "these results demonstrate a strong potential link between chronic TCE exposure and parkinsonism" (Gash *et al*., 2008). However, the authors acknowledged, "Still, the presence of possible comorbid factors needs to be carefully analyzed and is consistent with Carvey and colleagues' hypothesis positing that the progressive loss of dopamine neurons characterizing Parkinson's disease is due to multiple insults leading to the degeneration of the nigrostriatal dopamine system in the brain" (Gash *et al*., 2008). In addition, the authors noted that their study involved exposure doses that were substantially higher than typical occupational exposure levels in humans.

Moreover, the magnitude of loss of dopaminergic neurons (45%) and reduction of dopamine content (20%) in the SNpc was less than that required to produce clinical signs of PD in humans (60-80% and 70-80%, respectively) (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). Regarding the loss of SNpc dopaminergic neurons reported by Gash *et al*. (2008), US EPA (2011a) concluded the study "evaluated only a single dose level of TCE, so establishing a dose-response relationship is not possible. Consequently, these data are of limited utility in risk assessment because they do not establish the potency of TCE to damage dopamine neurons."

6.2.1.3 Liu *et al*. (2010)

Liu *et al*. (2010) exposed male Fischer 344 rats to 0, 200, 500, or 1,000 mg/kg-day TCE *via* oral gavage 5 days per week for 6 weeks. A total of 20.1, 25.6% and 40.6% losses of SNpc dopaminergic neurons were associated with exposures to 200, 500, and 1,000 mg/kg-day TCE, respectively, but the effect was only statistically significant at 500 and 1,000 mg/kg-day. Even at the highest dose, the magnitude of dopaminergic neuron loss (40.6%) was less than that required to produce clinical signs of PD in humans (60-80%) (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). The authors conducted all subsequent experiments at the highest dose only.

Exposure to 1,000 mg/kg-day TCE was associated with statistically significant decreased mitochondrial complex I activity, decreased levels of dopamine metabolites, increased markers of oxidative stress and inflammation, and accumulation of α-synuclein in SNpc neurons (Liu *et al*., 2010). In contrast, there was no decrease in dopamine levels in striatum, indicating that the surviving neurons maintained dopamine levels, and that there was no loss of neurons in extranigral brain regions. Collectively, these findings are inconsistent with PD.

In addition, inconsistent effects were observed by Liu *et al*. (2010) in motor function tests; TCE exposure significantly reduced motor performance and coordination as measured by rotarod test (at 5 and 6 weeks of TCE treatment, but not ≤ 4 weeks of treatment), but had no effect on spontaneous locomotor activity. Notably, Lock *et al*. (2013) indicated that the rotarod test "is not a good measure of behavior associated with [dopamine] depletion." Overall, Liu *et al*. (2010) concluded the results of their study demonstrated "some important features of Parkinsonism," but that the results "could be interpreted as a TCE-induced moderate injury in which there are no significant decreases of dopamine content in the striatum and no marked deficit of spontaneous locomotor activity in TCE-treated animals."

6.2.1.4 Liu *et al*. (2018)

Liu *et al*. (2018) exposed adult male C57BL/6 mice to 400 mg/kg-day TCE 5 days per week for 8 months *via* oral gavage. In the SNpc, TCE exposure was associated with a statistically significant loss of dopaminergic neurons (not "greater than 50%"), a 50% decrease of dopamine levels, a 72.1% decrease of dopamine metabolite levels, decreased mitochondrial complex I activity, and accumulation of α-synuclein. In tests of motor function, TCE exposure significantly decreased locomotion, exploration, coordination, and balance as measured by open field and rotarod tests. In contrast, there was no effect on dopamine receptor levels.

In addition, the authors measured the endogenous formation of 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) in brain, liver, and kidney of TCE-treated mice. The authors stated that TCE had reproduced "the neuropathological, neurochemical, and behavioral features of Parkinsonism," and that "TCE is likely to contribute significantly to the occurrence of PD in the general population" (Liu *et al*., 2018). Despite these findings, the authors concluded, "However, even prolonged administration of TCE

was insufficient for producing a greater than 50% loss of nigral dopamine neurons, indicating that additional comorbid factors would be needed for mimicking the profound loss of dopamine neurons seen in Parkinson's disease" (Liu *et al*., 2018). I conclude that, because the magnitude of loss of dopaminergic neurons and dopamine levels in SNpc were less than that required to produce clinical signs of PD in humans (60-80% and 70-80%, respectively) (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024), this study does not provide evidence that human exposure to TCE can cause PD.

6.2.1.5 De Miranda *et al*. (2021)

De Miranda *et al*. (2021) investigated whether TCE exposure increased activity of the leucine-rich repeat kinase 2 (LRRK2) gene, as mutations that increase LRRK2 activity are the most common genetic cause of familial and sporadic PD. Lewis rats were exposed to TCE *via* oral gavage as part of three cohorts involving different experimental conditions: in Cohort 1, males were exposed to 0 or 200 mg/kg-day TCE for 6 weeks; in Cohort 2, males and females were exposed to 0 or 200 mg/kg-day TCE for 1, 3, or 6 weeks; in Cohort 3, males were exposed to 0, 50, 100, 200, 400, or 800 mg/kg-day TCE for 3 weeks. PD-associated pathological and behavioral (*i.e*., motor function) effects were examined in cohort 1 animals, temporal loss of dopaminergic neurons was examined in Cohort 2 animals, and LRRK2 activity was examined in Cohort 3 animals. Dopamine content in the SNpc was not measured in any cohort.

In Cohort 1, TCE exposure was associated with a statistically significant loss of dopaminergic neurons in the SNpc (approximately 32%), increased markers of oxidative stress and inflammation, accumulation of α-synuclein in SNpc neurons, and reduced locomotor behavior (in two of three outcome measures) as measured by the open field test. In Cohort 2, a statistically significant loss of SNpc dopaminergic neurons was observed in males and females exposed to TCE for 6 weeks, but not for 1 or 3 weeks. Regarding the loss of dopaminergic neurons, the magnitude of loss (32%) was less than that required to produce clinical signs of PD in humans (60-80%) (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). Finally, in Cohort 3, increased markers of LRRK2 activation were only associated with exposure to doses ≥ 200 mg/kg-day. The authors concluded that the mechanism by which TCE may activate LRRK2 "is less clear" and that the extent that LRRK2 activation by chemicals may affect the dopaminergic system of humans carrying LRRK2 mutations "is unclear" (De Miranda *et al*., 2021).

Importantly, De Miranda *et al*. (2021) reported reduced growth in TCE-exposed rats compared to controls (Supplemental Figure 1 in De Miranda *et al*. [2021]).[16] For example, TCE-exposed rats in Cohorts 2 and 3 were approximately 4-5% smaller at the end of the exposure period compared to control animals. Because of evidence of systemic toxicity, the reported changes in neurological and behavioral outcomes in TCE-exposed rats observed in this study cannot be reliably attributed to TCE exposure.

6.2.1.6 Ilieva *et al*. (2022)

Ilieva *et al*. (2022) exposed female Lewis rats to 0 or 200 mg/kg-day TCE for 6 weeks *via* oral gavage and collected fecal samples to analyze the gut microbiome. The authors reported that changes in the abundance of gut microorganisms of the TCE-exposed rats shared some similarities with patterns of individuals with idiopathic PD. Ilieva *et al*. (2022) stated, "[W]e postulate that TCE exposure within contaminated drinking water could induce alterations of the gut microbiome that contributes to the chronic disease risk, including

[16] De Miranda *et al*. (2021) stated, "No significant body mass decrease was observed in any TCE Cohort," but the authors did not report statistical results for this analysis. Further, this conclusion is at odds with data that the study authors presented in Supplemental Figure 1.

idiopathic PD." However, this study did not assess motor function or any pathological outcomes in the SNpc or provide any evidence that that changes in the abundance of gut microorganisms can cause PD.

6.2.1.7 Ilieva *et al*. (2024)

Ilieva *et al*. (2024) conducted a follow-up study to De Miranda *et al*. (2021) to investigate whether TCE exposure increased activity of the LRRK2 gene. Ilieva *et al*. (2024) exposed female Lewis rats to 0 or 200 mg/kg-day TCE *via* oral gavage for either 3 weeks, or for 6 weeks with MLi2 (an inhibitor of LRRK2) from weeks 3 through 6. At 3 weeks of exposure, dopaminergic neuron number was the only pathological endpoint evaluated, and no changes were reported. At 6 weeks of exposure, there was a 45% loss of dopaminergic neurons in SNpc ($p < 0.0001$) and elevated markers of oxidative stress, mitochondrial dysfunction, and phagocytic activity by microglia ($p < 0.001$-0.0001). These effects were attenuated by treatment with MLi2. However, the magnitude of dopaminergic neuron loss (45%) was less than that required to produce clinical signs of PD in humans (60-80%) (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). This study did not assess effects on motor function or dopamine content in the SNpc.

6.2.1.8 Srivastava *et al*. (2024)

Srivastava *et al*. (2024) exposed male Wistar rats to 0 or 1,000 mg/kg-day TCE *via* oral gavage for: 1) 8 weeks, 2) 8 weeks with PD therapeutic compounds (Levodopa and Carbidopa) from weeks 4 through 8, or 3) 8 weeks with the antioxidant compound alpha pinene-loaded self-emulsifying nano-formulation (ALP-SENF) from weeks 4 through 8. Exposure to TCE was associated with locomotor impairment (*i.e*., decreased fall off time on rotarod, grip strength, postural stability and gait, step alternation, and forelimb locomotion) ($p < 0.0001$). In addition, TCE-exposed rats had altered levels of antioxidant enzymes ($p < 0.0001$) and elevated levels of a marker of lipid peroxidation ($p < 0.0001$), as measured in homogenized samples of the forebrain and cerebellum (not the SNpc, specifically). The authors stated that TCE exposure was also associated with "[s]ignificant neuronal loss" in the midbrain, but the authors did not report the magnitude of loss or discuss statistical significance. These effects were attenuated by treatment with Levodopa and Carbidopa, or ALP-SENF. This study had several limitations: dopamine content in the SNpc, and the magnitude and statistical significance of dopaminergic neuron loss caused by TCE, were not assessed; the nonquantitative evaluation of dopaminergic neurons was not conducted in the SNpc; only one dose was tested; and the relevance of the extremely high dose tested to humans is not clear.

Intraperitoneal Injection

6.2.1.9 Keane *et al*. (2019)

Keane *et al*. (2019) administered TCE (0 or 1,000 mg/kg-body weight [bw]) or TaClo (0 or 2 mg/kg-bw) *via* i.p. injection twice weekly for 8 weeks to male and female C57BL/6 mice of wildtype background or that overexpressed mutant human α-synuclein (A30P). Dopamine content in the SNpc was not measured in this study.

TCE exposure caused a statistically significant loss of dopaminergic neurons in the SNpc in wildtype and A30P mice of approximately 50% and 70%, respectively. TaClo exposure was also associated with a statistically significant loss of dopaminergic neurons in the SNpc, however, the percentage of neurons lost was not reported, nor whether dopamine levels were maintained by the surviving neurons. In contrast, TCE and TaClo exposure did not affect motor function as assessed by rotarod and pole tests, fore paw grip strength, or spatial learning and memory as assessed by Barnes maze.

The authors stated, "TCE or TaClo did not appear to lead to acceleration of motor or cognitive deficits in either wild type or A30P mutant mice, potentially because of the modest reductions of [dopamine] neuronal number in the SNpc" (Keane *et al*., 2019). The authors concluded, "It is possible that the levels of [dopamine] cell death in the SNpc of treated animals are insufficient to cause motor dysfunction since over 70-80% SNpc cell death is required before behavioural deficits are seen" (Keane *et al*., 2019).

Summary

Overall, only one rat and one mouse bioassay have evaluated TCE inhalation and PD-associated pathological outcomes, but this study used only a very high dose in each species, and the magnitude of dopaminergic neuron loss was below levels required to produce clinical signs of PD in humans. Some PD-associated pathological outcomes were observed in rats and mice exposed to very high doses of TCE *via* oral gavage or i.p. injection for subchronic durations, but these exposure conditions are not relevant to typical environmental or occupational exposures to TCE in humans. In addition, although subchronic oral TCE exposures in rats and mice were associated with loss of dopaminergic neurons and reduced dopamine levels in the SNpc, the magnitude of loss was less than that required to produce clinical signs of PD in humans. Collectively, the evidence from subchronic experimental animal studies does not support a causal relationship between TCE exposure and PD in humans.

6.2.2 Subacute Studies

I identified three subacute bioassays of TCE that evaluated pathological outcomes associated with PD (one in rats and two in mice). Loss of dopaminergic neurons in the SNpc was reported in one i.p. injection study in mice, but not in another mouse i.p. injection study or in an oral gavage study in rats. In addition, none of the subacute studies reported effects on motor function, none measured dopamine content in the SNpc, and none examined inhalation exposure. All subacute oral and i.p. injection studies are discussed below and summarized in Table 6.1 and Attachment E, Tables E.4 and E.5.

6.2.2.1 Sauerbeck *et al*. (2012)

Sauerbeck *et al*. (2012) exposed male Fischer 344 rats to TCE *via* oral gavage at 0 or 1,000 mg/kg-day for 1 or 2 weeks. PD-associated pathological outcomes were examined in the SNpc and striatum, two brain regions involved in the nigrostriatal dopamine system and the etiology of PD. Statistically significant 75% inhibition of mitochondrial complex I activity was observed in the striatum, whereas there was no effect on complex I activity in the SNpc. In addition, TCE exposure had no effect on numbers of SNpc dopaminergic neurons, or motor function and coordination (as measured by a rotarod test, and paw placement on a plastic cylinder).

6.2.2.2 Guehl *et al*. (1999)

Guehl *et al*. (1999) exposed male OF1 mice to TCE *via* i.p. injection at 0 or 400 mg/kg-day 5 days per week for 4 consecutive weeks. A statistically significant 50% loss of dopaminergic neurons in SNpc was reported. However, there was no effect on motor function. As stated by the authors: "The trichloroethylene-treated mice presented no parkinsonian motor abnormalities." Overall, regarding the loss of SNpc dopaminergic neurons reported by Guehl *et al*. (1999), US EPA (2011a) concluded the study "evaluated only a single dose level of TCE, so establishing a dose-response relationship is not possible. Consequently, these data are of limited utility in risk assessment because they do not establish the potency of TCE to damage dopamine neurons."

6.2.2.3 Otsuki *et al*. (2016)

Otsuki *et al*. (2016) administered TCE *via* i.p. injection at 0 or 500 mg/kg-bw, 3 days per week for 4 weeks, to male C57BL/6 mice of wildtype background or null for the antioxidant enzyme superoxide dismutase 1 ($Sod1^{-/-}$). Under these experimental conditions, the authors reported statistically significant lower motor function (as measured by rotarod and open field tests), but there were no effects of TCE on numbers of dopaminergic neurons in the SNpc. The authors noted that the results of the current study were inconsistent with the results of Guehl *et al*. (1999) and Liu *et al*. (2010) potentially due to difference in experimental conditions: "The inconsistent results regarding cell death and monoamine metabolites among the studies might be partly attributed to the difference in the amount of TCE used, species, or the strain of rodents used" (Otsuki *et al*., 2016).

Collectively, subacute animal exposure studies do not support a causal association between TCE exposure and PD.

6.2.3 Conclusions

No chronic animal bioassays have examined PD-associated pathological or behavioral outcomes. In subchronic and subacute studies, some PD-associated pathological effects in the SNpc (*e.g.*, α-synuclein accumulation, loss of dopaminergic neurons and/or depletion of dopamine, inhibition of mitochondrial complex I activity) or behavioral effects (*e.g.*, decreased motor function or coordination) were observed in rats and mice. However, the oral and i.p. injection studies involved very high doses (*i.e.*, 200 to 1,000 mg/kg-day) that are not relevant to human environmental or occupational exposures to TCE (*e.g.*, see Gash *et al*. [2008]). In addition, although subchronic animal bioassays reported loss of dopaminergic neurons and/or decreased dopamine content in the SNpc associated with TCE exposures, the magnitude of loss was less than that required to produce clinical signs of PD in humans (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). Also, some behavioral effects were not consistent within or across studies (*e.g*., De Miranda *et al*., 2021). I conclude that evidence from experimental animal studies does not support a causal relationship between TCE exposure and PD in humans.

6.3 Mode of Action

No human studies have examined whether TCE exposure causes dopaminergic neuron disruption (US EPA, 2011a). In rodents, some subchronic studies reported pathological effects on dopaminergic neurons in the SNpc associated with exposure to high doses of TCE administered orally or *via* i.p. injection. However, it is unclear whether TCE itself, or a metabolite of TCE, caused these effects or whether these effects would occur after exposure to lower doses (Lock *et al*., 2013).

Beginning in the 1990s, some research groups posited the so-called "TaClo hypothesis," which suggested that the formation of chlorinated TaClo, a compound that can be formed from the metabolite of TCE, chloral, can contribute to PD-like symptoms (US EPA, 2011a). US EPA (2011a) stated, "Some research groups have hypothesized that Parkinson-like symptoms resulting from TCE exposure may occur through the formation of TaClo, but not enough evidence is available to determine if this mechanism occurs." Similarly, Lock *et al*. (2013) concluded that "any link between TaClo formation from TCE and damage to the SNpc seems tenuous and probably misguided." To date, only one experimental animal study has reported the formation of TaClo in mouse brain, liver, and kidney tissues at very low levels (parts per trillion [ppt]) after oral gavage treatment with high levels of TCE (400 mg/kg-day) (Liu *et al*., 2018). Regarding

the results of Liu *et al*. (2018), De Miranda and Greenamyre (2020) stated, "These data indicate that chronic exposure to TCE may be required to produce TaClo at a concentration that contributes to dopaminergic toxicity, however, more studies are needed to assess whether TaClo production is the ultimate dopaminergic toxicant following chronic TCE exposure." Further, De Miranda and Greenamyre (2020) concluded, "It is unknown whether TCE exposure produces high enough TaClo concentrations in the brain to cause significant damage to dopaminergic neurons." In the most recent risk evaluation of TCE conducted by US EPA in 2020, there is no discussion of TaClo or the "TaClo hypothesis" (US EPA, 2020a).

Some studies have examined effects of TaClo itself administered *in vitro* or *in vivo* (*via* direct i.p. injection, injection into brain, or oral route). Evaluation of these studies is outside the scope of my report. However, I note that, in general, findings from these studies are inconsistent and suggest that TaClo does not have specificity for the dopaminergic system and is not selectively toxic to dopaminergic neurons (Storch *et al*., 2006; Lock *et al*., 2013). This is important because human PD is characterized by a selective toxicity to dopaminergic neurons in the SNpc. Thus, I conclude that the scientific evidence does not support TaClo formation as a causal factor for PD.

Overall, there is no evidence that TCE exposure can cause dopaminergic neuron loss or decrease dopamine levels in humans (US EPA, 2011a), as it is limited to animal studies of subchronic and subacute duration involving oral or i.p. injection exposures to high doses, and a single subchronic inhalation study that involved exposure concentrations of uncertain relevance to human environmental or occupational exposures. Moreover, the mechanism by which TCE may affect the dopaminergic system in humans (*i.e.,* the specific mechanism by which TCE may cause dopaminergic neuron death and alter dopamine content in SNpc) remains unclear (De Miranda *et al*., 2021).

6.4 Agency Reviews

6.4.1 Institute of Medicine

IOM reviewed the associations between solvent exposures and PD in the context of the Gulf War and Camp Lejeune. As discussed below, most of the studies included were not specific to TCE and are therefore not included in my evaluation.

In an assessment of insecticides and solvents in the context of the Gulf War, IOM (2003) determined that only Hertzman *et al*. (1994) and Seidler *et al*. (1996) were "sufficiently rigorous in design" to provide evidence on solvent exposure and PD. Both studies reported associations, but IOM (2003) concluded that "both studies were likely to have been subject to recall bias" and concluded "there [was] inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and Parkinson's disease."

In the assessment of potential health effects at Camp Lejeune, NRC (2009) identified three additional studies of solvents and PD. McDonnell *et al*. (2003) conducted a case-control study of men in the United Kingdom, and NRC (2009) said, "The study included a small number of cases and lacked information on other possible risk factors or confounders." Dick *et al*. (2007) was a case-control study conducted in five European countries that included 767 prevalent cases and 1,989 controls. NRC (2009) said, "This study is characterized by a large number of subjects and provided no evidence of an association between solvent exposure and Parkinson disease." Finally, NRC (2009) included a cluster investigation of occupational exposure to TCE and PD or parkinsonism by Gash *et al*. (2008) and acknowledged "the significance of the study is difficult to judge" because of its design. In fact, Gash *et al*. (2008) stated, "It is important to recognize that this study was not a large-scale epidemiological investigation designed to address recall, case

finding, or other sources of bias." Similarly, Dorsey *et al*. (2023) noted, "The evidence linking possible exposure to TCE in these cases is circumstantial." NRC (2009) "conclude[d] that there continue[d] to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and Parkinson disease."

Congress passed the Honoring America's Veterans and Caring for Camp Lejeune Families Act, also called the Janey Ensminger Act (P.L. 112-154), in 2012 (IOM, 2015). The VHA drafted clinical guidance to help determine which medical conditions should be covered by the act. IOM (2015) conducted a review of the "VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation." In this review, the IOM Committee identified four additional studies of solvents and PD that had been published since the NRC (2009) report. This included Goldman *et al*. (2012), Bove *et al*. (2014a,b), and the review by Lock *et al*. (2013). IOM (2015) stated:

> Despite the limitations of these studies, such as lack of statistical significance, the potential for recall bias, and the lack of incidence data pertaining to Parkinson's disease, the committee recommends including Parkinson's disease as an outcome associated with exposure to TCE and PCE. Because of the slow onset of Parkinson's disease, patients developing it years after their exposure, regardless of their age at exposure, may have not had symptoms at the time of exposure.

IOM (2015) acknowledged that "Lock *et al*. (2013) concluded that neither toxicologic nor epidemiologic studies present clear evidence that any specific solvent or class of solvents is an established cause of Parkinson's disease." Still, it concluded that PD is associated with TCE and PCE based on Goldman *et al*. (2012), Bove *et al*. (2014a,b), NRC (2009) and US EPA (2011a), finding "TCE and similar solvents may have potential etiologic relevance in the development of Parkinson's disease" (IOM, 2015).

However, except for Gash *et al*. (2008), which conducted a cluster investigation of TCE exposure and PD, the studies reviewed by NRC (2009) did not evaluate TCE or PCE specifically and, importantly, did not provide evidence of causation for any exposure to solvents and PD. There is no indication that US EPA (2011a) evaluated any additional epidemiology studies besides those reviewed by NRC and IOM (NRC, 2009; IOM, 2015). As discussed below, US EPA (2011a) also acknowledged evidence is limited with respect to a MoA for TCE exposure. Overall, IOM (2015) does not suggest that an association between TCE and PD is supported by the evidence as a whole, but rather that PD be included on a list of outcomes "associated with exposure to TCE and PCE" because evidence is inadequate to draw conclusions.

6.4.2 ATSDR

In a 2017 review of drinking water contaminants at Camp Lejeune, ATSDR concluded "that the epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above. However, given the strong supporting mechanistic evidence for TCE, ATSDR concludes that there is equipoise and above evidence for causation for TCE and Parkinson disease" (ATSDR, 2017a). With respect to animal and mechanistic information, ATSDR (2017a) cited only Gash *et al*. (2008), Zaheer and Slevin (2011), and the review by Lock *et al*. (2013). ATSDR (2017a) said Lock *et al*. (2013) concluded, "On balance, the convergence of toxicological and epidemiological research suggests a plausible association between TCE exposure and PD." However, this quote is misleading, as Lock *et al*. (2013) concluded:

> At present, there is no consistent evidence from either the toxicological or epidemiologic perspective that any specific solvent or class of solvents is a cause of PD. Future

toxicological research that addresses mechanisms of nigral damage from TCE and its metabolites, with exposure routes and doses relevant to human exposures, is recommended.

In 2019, others at ATSDR reviewed the toxicity of TCE in a Toxicology Profile. This document only cited the cohort studies conducted by Goldman *et al*. (2012) and Bove *et al*. (2014a) in its evaluation of PD (ATSDR, 2019a). Regarding Goldman *et al*. (2012), ATSDR noted that "ever exposure to trichloroethylene was associated with a significantly increased risk" (ATSDR, 2019a). Regarding Bove *et al*. (2014a), ATSDR noted that the authors "did not calculate SMRs for Parkinson's disease because less than five cases were observed" (ATSDR, 2019a). Further, ATSDR noted that in its retrospective cohort morbidity study of Camp Lejeune marines, "there was no indication of increased risk of amyotrophic lateral sclerosis (ALS), multiple sclerosis, or Parkinson's disease in any trichloroethylene cumulative exposure group (ATSDR 2018)" (ATSDR, 2019a). The ATSDR (2018b) morbidity study is discussed in more detail in Section 5.1.1. ATSDR (2019a) did not discuss any animal or mechanistic studies that examined the potential association of TCE with PD. ATSDR (2019a) did not conclude that TCE is a known cause of PD.

6.4.3 US EPA

In 2011, US EPA (2011a) noted that "loss of dopaminergic neurons in the *substantia nigra* may be one of the potential mechanisms involved in the clinical psychomotor effects that is observed following TCE exposure," and that "[l]oss of dopaminergic neurons in the *substantia nigra* also occurs in patients with Parkinson's disease." US EPA (2011a) also reported that TCE-induced effects on dopaminergic neurons were reported in only two animal studies (Gash *et al*., 2008; Guehl *et al*., 1999), and "[t]here are no human studies that present evidence that TCE exposure results in dopamine neuron disruption." With respect to a potential MoA for TCE-induced PD, US EPA (2011a) concluded, "Some research groups have hypothesized that Parkinson-like symptoms resulting from TCE exposure may occur through the formation of TaClo, but not enough evidence is available to determine if this mechanism occurs."

US EPA's most recent evaluation of TCE, published in November 2020, stated that "several newer epidemiological studies have found an association between TCE exposure and neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (Bove *et al.*, 2014a) and Parkinson's disease (Bove *et al.*, 2014b; Goldman *et al*., 2012)" (US EPA, 2020a). The risk evaluation provided no further discussion of the epidemiology studies of TCE and PD or whether any associations were likely causal. As discussed in Section 6.1.1, these studies do not provide evidence of causation. US EPA (2020a) also did not discuss any animal or mechanistic studies (including studies that evaluated TaClo) that examined the potential association of TCE with PD. US EPA did not conclude that TCE is a cause of PD.

6.4.4 Conclusions

ATSDR (2017a), which was written by one person over a period of 6 weeks, concluded that "epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above," but "there is equipoise and above evidence for causation for TCE and Parkinson disease" based on "strong supporting mechanistic evidence." This conclusion is inconsistent with all other agency reviews, including the ATSDR Toxicological Profile, none of which concluded that TCE is a known cause of PD (ATSDR, 2017a, 2019a; IOM, 2003, 2015; NRC, 2009; US EPA, 2011a, 2020a).

6.5 Evidence Integration

Few epidemiology and toxicity studies have evaluated TCE and PD. The small number of relevant epidemiology studies had higher quality outcome assessments and study designs, with limited evidence for

selection bias and most accounted for temporality. Control for potential confounders varied across studies. No study, including those that assessed risks at Camp Lejeune, had adequate information on individual exposures, calling into question the reliability of reported risk estimates. While animal studies were higher quality with respect to reporting, confounding, and attrition, they were lower quality with respect to allocation, chemical administration and characterization, and outcome sensitivity and specificity. They were also of lower quality for human health risk assessment because of the animal models (which do not exactly mimic the etiology, progression, and pathology of human PD), high doses, and, most only evaluated one dose. Keeping these study strengths and limitations in mind, I evaluated the available evidence as a whole in the context of Bradford Hill's considerations. I conclude that the evidence does not support a causal association between TCE and PD.

1. **Strength of Association.** There is no consistent evidence of strong associations. Risk estimates ranged from 0 to 6.1. Most of the estimates > 2 were based on very low numbers of exposed cases (< 10) and had very wide CIs. These wide CIs lack precision and add uncertainty regarding the true magnitude of risk.
2. **Consistency.** While statistically significantly increased risks were reported in three epidemiology studies of TCE exposures and PD, only one study reported consistently statistically significant increased risks within the study. Five other studies (some of overlapping populations, including Camp Lejeune) did not show consistent statistically significantly increased risk ratios. Risk estimates across studies ranged widely, from 0 to 6.1.
3. **Specificity.** There is no evidence to suggest that there is a specific relationship between TCE and PD.
4. **Temporality.** Most of the epidemiology studies reviewed assessed exposure to TCE in a time period prior to disease occurrence (although indirectly). Further, while the exact relevant time window of exposure and latency period for PD is unknown, the periods of follow-up in the cohort studies were likely sufficient to account for temporality.
5. **Dose-Response.** ATSDR (2018b), Sallmén *et al*. (2023), and Goldman *et al*. (2012) evaluated PD risk by level of TCE exposure and results were inconsistent. Sallmén *et al*. (2023) and ATSDR (2018b) did not report any consistent increased risks with an increasing level of TCE; neither reported p-trends. Goldman *et al*. (2012) reported statistically significant increased risks of PD with increases in tertile of duration of exposure or cumulative exposure in linear models, but there was a very small number of exposed cases in this study and all CIs were very wide.
6. **Biological Plausibility.** No chronic exposure studies of TCE have examined PD-associated pathological or behavioral outcomes. Some PD-associated pathological outcomes were observed in rats and mice dosed with very high levels of TCE *via* inhalation exposure, oral gavage or i.p. injection for subchronic durations, but the animal models do not exactly mimic the etiology, progression, and pathology of human PD, and the exposure conditions (high doses and often i.p. exposure route) are not relevant to typical environmental or occupational exposures to TCE in humans, including at Camp Lejeune (Gash *et al*., 2008; Aleksunes and Eaton, 2019). Even if evidence suggested a biologically plausible association at high doses, that does not provide evidence for biological plausibility for low-level environmental exposures.

7. **Coherence.** Because of their methodological limitations and lack of consistency, epidemiology studies do not provide support for an association between TCE and PD. It is generally understood that there is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD (Tieu, 2011; Lock *et al*., 2013; Jiang and Dickson, 2018; El-Gamal *et al*., 2021; Pang *et al*., 2019). Although high-dose subchronic TCE exposure studies in rats and mice reported a loss of dopaminergic neurons in SNpc, the magnitude of loss was less than that generally thought to be required to produce clinical signs of PD in humans (60-80%) (Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). There is no proven mechanism by which TCE may affect the dopaminergic system in humans.
8. **Experiment.** There is no available experimental evidence in humans.
9. **Analogy.** It has been suggested that TCE can produce TaClo, which may be analogous to MPTP in that they both can stimulate mitochondrial dysfunction, oxidative stress, and inflammation. However, to date, only one animal study has experimentally detected the endogenous formation of TaClo *in vivo* following subacute oral exposure (Liu *et al*., 2018). This study evaluated oral exposure doses (250-1,000 mg/kg-day) that are much higher than typical human exposures, including at Camp Lejeune. No study has examined whether TaClo may be endogenously formed in humans following exposure to TCE *via* chronic ingestion or inhalation. Also, TCE was not found to lower dopamine levels in the SNpc in most studies. For these reasons, I conclude that, as a whole, the scientific evidence does not support the hypothesis that TCE can contribute to PD *via* the formation of TaClo. My opinion is consistent with that of US EPA (2011a), which stated, "Some research groups have hypothesized that Parkinson-like symptoms resulting from TCE exposure may occur through the formation of TaClo, but not enough evidence is available to determine if this mechanism occurs." In its most recent evaluation of TCE, US EPA did not discuss TaClo (US EPA, 2020a).

6.6 Conclusions

Few epidemiology studies have evaluated associations between TCE exposure and PD. These studies have several methodological limitations (most notably indirect exposure estimates); as such, they do not provide evidence for a causal association. There is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD. While subchronic- and subacute-duration experimental animal studies have reported some PD-associated pathological or behavioral effects in rats and mice, most studies only tested one dose and therefore were unable to evaluate dose-response, and the doses used in these studies (200-1,000 mg/kg-day, 50 or 100 ppm) are much higher than typical human exposures, including at Camp Lejeune. Regardless, even at these high exposures, the magnitudes of effects (specifically on dopaminergic neuron loss and reduced dopamine levels in the SNpc) were below those that have been shown to be necessary to produce clinical signs of PD in humans. Finally, no scientific or regulatory agency has concluded that there is a known causal association between TCE exposure and PD in humans based on reviews of epidemiology, animal, and MoA studies.

Because the epidemiology studies are not of high quality and do not consistently show an association, and animal studies do not provide evidence of causation in humans, my opinion is that, as a whole, the currently available evidence does not support a causal association between TCE exposure and PD.

7 PCE and PD

PCE, also known as PERC, perchloroethylene, or tetrachloroethylene, is a colorless, nonflammable, and volatile liquid (ATSDR, 2019b). While it can occur naturally, PCE is most frequently manufactured for use as a solvent in the dry-cleaning, textile, automotive, and metal industries 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 (ATSDR, 2019b; IARC, 2014b; US EPA, 2012, 2020b). PCE can degrade in the environment to TCE, and TCE may be present as a contaminant in products containing PCE (ATSDR, 2019b).

Individuals can be exposed to PCE from contaminated air, water, food, and soil (ATSDR, 2019b; US EPA, 2012). PCE has been one of the most commonly detected chemicals in indoor environments, due to its use in consumer products, building materials, and dry-cleaning products, as well as its presence in drinking water and ability to vaporize (ATSDR, 2019b). PCE can be absorbed into the body after inhalation, ingestion, or dermal contact (ATSDR, 2019b; US EPA, 2012). PCE is quickly absorbed into the bloodstream, and is quickly excreted *via* exhalation (ATSDR, 2019b; US EPA, 2012). PCE that is not quickly exhaled can be metabolized to breakdown products and excreted in the urine (ATSDR, 2019b; US EPA, 2012). PCE has an affinity for fat and can distribute to multiple organs, including the liver, kidney, brain, lung, and heart (ATSDR, 2019b; US EPA, 2012). The half-life of PCE in the body is about 3 days (ATSDR, 2019b).

Few epidemiology studies have evaluated associations between PCE exposure and PD. These studies have mixed results and several methodological limitations and, as such, do not provide evidence for an association. PCE has not been evaluated in animal studies. No scientific or regulatory agency has concluded that PCE is a known cause of PD. The scientific evidence regarding PCE exposure and PD is discussed below.

7.1 Epidemiology

I reviewed the studies considered by US EPA (2011a, 2020a) and ATSDR (2017a, 2019a), and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). I identified four cohort and three case-control studies in six unique populations that examined the association between PCE exposure and PD, and a few case studies and case series.[17] I review here all Camp Lejeune studies that specifically evaluated PCE exposures, even if overlapping, for completeness. I do not discuss Camp Lejeune studies in this section that did not evaluate PCE-specific exposures (*e.g.*, exposure was assumed if a person was stationed at Camp Lejeune). All of the epidemiology studies included individuals who were potentially exposed to both PCE and TCE, as well as other chemicals, from drinking water, hobbies, or at the workplace, so it was not possible to tease out associations for either chemical alone. Most of the risk estimates reported in these studies were identical for PCE and TCE, and not specific to either chemical.

[17] There are several case studies and case series of individuals with PD who had some exposure to TCE and PCE at some point in their lives (Dorsey *et al*., 2023). These studies are discussed in Section 5.1.3. Because they do not provide any information on causation, they are not reviewed further here.

I summarize the characteristics, results, and quality of the epidemiology studies related to PCE exposure and PD below and in Attachment F, Tables F.1-F.4, and Attachment C, Table C.1. Overall, primarily because of their methodological limitations, these studies do not provide evidence for a causal association between PCE exposure and PD.

7.1.1 Cohort Studies

I identified four cohort studies that evaluated the relationship between PCE exposure and PD, all of which were conducted in the US (Attachment F, Tables F.1 and F.2).[18] Two of these studies examined this relationship in overlapping populations among civilian or US Marines and Navy personnel at Camp Lejeune potentially exposed to PCE *via* contaminated water (mortality: ATSDR [2018b]; Bove *et al*. [2014a]; incidence: ATDSR [2018b]). I discuss these studies in detail in Section 5. The other cohort studies evaluated PD mortality risk among microelectronics and business machine facility employees occupationally exposed to PCE (Silver *et al*., 2014), and PD risk among partners at a law firm located across the street from a large dry cleaner in Rochester, New York (Dorsey *et al*., 2024).

None of the cohort studies assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Table C.1). In the Camp Lejeune studies, exposures were based on the estimated monthly average PCE concentration in groundwater while participants lived or worked on base. There was no information on water consumption or actual individual exposures to PCE or other chemicals in drinking water, including TCE. Silver *et al*. (2014) only reported results for the entire population of participants who worked at the microelectronics and business machine facility; they did not report any risk estimates for PCE exposure and PD. Dorsey *et al*. (2024) considered partners exposed if they had been employed at the law firm for over 1 year. Additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between PCE exposure and PD.

Bove *et al*. (2014a)

Overview

Bove *et al*. (2014a) retrospectively evaluated PD deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985, and who had been potentially exposed to PCE-contaminated drinking water on base. Between 1979 and 2008, there were five PD deaths in the cohort. There was no statistically significant increased risk of PD mortality in those with estimated cumulative exposures to PCE greater than the median compared to those with estimated cumulative exposures less than the median (HR = 2.68, 95% CI: 0.22-33.28). The authors reported similar results in models of $\log_{10}$ continuous cumulative PCE exposure.

Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 2%), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the study, less than 15% of the study population had died, and only a small number of PD deaths were observed (n = 5), which limits precision of the estimated associations.

[18] In addition to these four studies, Bove *et al*. (2014b) evaluated health risks in 154,932 Marines and Navy personnel stationed at Camp Lejeune during the time of the water contamination, using similar methods to those used in Bove *et al.* (2014a). There were fewer than five PD deaths observed, so they did not report analyses of PCE exposure and PD.

Exposure Assessment. Potential exposures were estimated based on groundwater fate and transport models of the monthly average concentrations of PCE in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. These direct measurements are more reliable than exposure estimates that are not based on any quantitative information, but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely.

Outcome Assessment. The study assessed PD mortality, which is weaker than examining PD incidence, because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e.*, SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for sex and occupation (blue *vs.* white collar). The authors considered but did not control for age because the adjusted results differed from the unadjusted results by less than 10%. The authors did not consider or control for genetic factors, family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly to use as a proxy for other potential occupational exposures, it is unclear if they analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

Silver *et al*. (2014)

Overview

Silver *et al*. (2014) identified 43 PD deaths among 34,494 employees of a microelectronics and business machine facility, where PCE was used in substrate manufacturing, with increasing use after 1974. The authors reported no statistically significant increased risk of PD deaths among male hourly (SMR = 0.87, 95% CI: 0.54-1.34), male salaried (SMR = 1.21, 95% CI: 0.73-1.89), female hourly (SMR = 0.73, 95% CI: 0.15-2.14), or female salaried (SMR = 0.00, 95% CI: 0.00-21.8) employees.

Quality Considerations

Study Population. The study used appropriate comparison groups, and likely had low attrition because follow-up for PD deaths after employment used reliable government records (SSA, NDI, and IRS). This cohort was relatively young (mean age at hire was in the mid-20s and average duration of follow-up was approximately 26 years), so only a small number of deaths had occurred by the end of the follow-up, limiting the precision of the estimated effect estimates.

Exposure Assessment. Exposure characterization was based solely on employment at the facility without consideration of actual exposures or exposure intensity.

Outcome Assessment. As noted above, the study used reliable government records (SSA, NDI, and IRS) to identify deaths, but PD mortality is not a good surrogate for PD incidence, because PD is not a fatal disease.

Covariates Considered. The authors controlled for age and sex, but did not consider or control for genetic factors, family history of PD, heavy alcohol intake, or smoking, which could have resulted in uncontrolled confounding. The authors only considered covariates at a single time point and the amount of missing covariate data was not reported, which further limits the ability to fully interpret the results.

Temporality. Occupational histories were collected separately from outcome data and the appropriate windows of exposure (*e.g.*, 10-year lag) were considered.

ATSDR (2018b)

Overview

In population that overlapped with Bove *et al*. (2014a), ATSDR (2018b) conducted a health survey from 2011 to 2012 that collected information on PD and lifestyle and demographic factors from 50,684 Marines and Navy personnel and 2,168 civilian employees stationed or employed at Camp Lejeune between 1972 and 1985. The authors compared PD incidence in Camp Lejeune to incidence in 8,615 Marines and Navy personnel or 1,425 civilian employees at Camp Pendleton. They also compared PD incidence by levels of exposure to PCE within the Camp Lejeune cohort. The authors reported no increased risks of PD in Marines and Navy personnel stationed at Camp Lejeune with any level of cumulative PCE exposure compared to Marines and Navy personnel at Camp Pendleton (low OR = 0.94, 95% CI: 0.51-1.71; medium OR = 0.54, 95% CI: 0.27-1.05; high OR = 1.22, 95% CI: 0.57-2.61). The authors reported statistically significant increased risk of PD in civilians employed at Camp Lejeune who had medium levels of cumulative exposure (OR = 3.47, 95% CI: 1.18-10.22) compared to civilians at Camp Pendleton, but not for low (OR = 2.78, 95% CI: 0.87-8.94) or high (OR = 2.86, 95% CI: 0.67-12.13) levels of exposure. There were similar patterns, but no statistically significant associations, reported for medium or high levels of exposure compared to low levels for Marines and Navy personnel or civilians in internal analyses.

Quality Considerations

Study Population. This study used appropriate comparison groups, but selection bias is likely. 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 authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

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

> because they were aware of the contaminated drinking water and believed they were affected by their exposures.

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

Exposure Assessment. Exposures to PCE were estimated based on groundwater fate and transport and water distribution system models coupled with historical occupation codes, period and duration of employment or residence, and workplace or residence location. These PCE-specific estimates are more reliable than exposure estimates that are not based on any quantitative information (*e.g.*, assignment on base), but without a direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption/exposure data), it is still likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures 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 exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations.

In a deposition, Dr. Bove (2024a) states, "The Marine Corps…didn't know, where barracks were on base, where units were barracked on base. And we relied on CAP [community assistance panel] members plus people they knew who had that memory…" Dr. Bove (2024a) also stated that they were not able to take into account a Marine's deployment off base and so they assumed that the DMDC data represented a continuous presence at Camp Lejeune, raising more concerns over 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al*., 1991) or multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed that nondifferential exposure measurement error could lead to bias towards or away from the null in a recent deposition, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

Outcome Assessment. Cases were confirmed using medical records or death certificates, but initial reliance on self-reported cases could have resulted in some missed cases. There were a small number of PD cases in the civilian population (n = 20), which may have resulted in risk estimates with reduced

precision. This analysis also focused on PD incidence, which is more informative than analyses evaluating mortality, since PD is not a fatal disease.

Covariates Considered. The authors only controlled for sex in their analyses. They considered but did not control for age, smoking, alcohol, or other potential occupational exposures or chemical exposures because adjusted results differed from unadjusted results by less than 10%. The authors did not consider or control for genetic factors or family history of PD. Covariate data were collected at a single timepoint *via* self-report and smoking, alcohol consumption, and other occupational exposures were missing for more than 5% of participants, increasing the likelihood of biased results.

Temporality. The study exposure and outcome periods overlapped, with follow-up beginning coincident with first exposure (*i.e.,* exposures could continue to occur after follow-up began). Some participants were followed for up to 40 years, but the authors did not consider a latency period.

Dorsey *et al*. (2024)

Study Description

Dorsey *et al*. (2024) retrospectively evaluated PD among 79 partners at a law firm in an office tower (*i.e*., the tower cohort) across from a large dry cleaner in Rochester, New York. The dry cleaner operated between 1950 and 1994, and in 1992, TCE, PCE and other chemicals[19] were found in the surrounding soil. The flow of groundwater was determined to be from the dry cleaner toward the office tower in which the law firm operated, potentially exposing the building occupants. Partners included in the study were employed at the firm for ≥ 1 year between 1968 and 2001. Dorsey *et al*. (2024) identified four cases of PD (5.1%) in the tower cohort through March 2023. The cumulative incidence (referred to as prevalence) of PD in the tower cohort was statistically significantly greater than what would be expected based on rates in the general population (1.7%) ($p = 0.01$), but not greater than what was observed in a comparison group of attorneys (1.3%) recruited from the local bar association's newsletter, flyers, and word of mouth ($p = 0.21$).

Quality Considerations

Study Population. The study did not use appropriate comparison groups. The characteristics of the tower cohort and the two comparison groups were very different. The tower cohort was comprised solely of partners in a law firm (*i.e*., highly educated), were 89.9% male, 97.3% white, 20.8% veterans, and 50% retired. These factors were not similar (except for educational attainment) compared to the comparison group and were likely very different from the characteristics of the general population. Participants in the tower cohort could be dead or alive, while participants in the comparison group were alive. Participation rates also varied, with the tower cohort having a participation rate of 96.3%, while only 63% of attorneys in the comparison group were eligible and participated. It is not known how those who did not participate differed from those who did.

Exposure Assessment. Because employment at the law firm for over 1 year was the only criteria for being considered exposed to TCE or PCE, there were no missing data on exposure. However, there was no consideration of actual individual-level exposures. Dorsey *et al*. (2024) did not report when the contamination started, only that the dry cleaner operated from 1950 to 1994, and that an environmental

[19] Dorsey *et al*. (2024) reported that other chemicals at the site "included methylene chloride, chloroform, chlorobenzene, 1,4-dichlorobenzene, 1,1,2,2-tetrachloroethane, cis 1,2-dichloroethene, 1,3,5- and 1,2,4–trimethylbenzene, isopropylbenzene, n-propylbenzene, sec-, and tert-butylbenzene, acetone, ethylbenzene, isopropylbenzene, naphthalene, toluene, p-isopropyltoluene, m-o-and p-xylene, and Stoddard solvent." These chemicals were not measured in the groundwater "because the groundwater at the site was not used for drinking" (Dorsey *et al*., 2024).

assessment found contaminated soil around the dry cleaner in 1992. There was a parking garage underneath the tower, and it was reported that "TCE, PCE, or other chemicals were still found in the exhaust gas from the garage ventilation system until the system was shut down in 2003" (Dorsey *et al*., 2024). There was no information on whether there was any potential exposure outside of the garage, how long the garage had been contaminated, or who in the tower cohort used the garage, how frequently, or what the exposure levels were in the garage over time.

Outcome Assessment. The study assessed cumulative incidence of PD (referred to as prevalence in the study), but deceased cases were included in the tower cohort, but all participants in the comparison group were alive at the time of the study, potentially biasing results. Cases were initially self-reported but confirmed using medical records and clinical assessments of PD, such as the Gelb Criteria for the Diagnosis of Parkinson's Disease.

Covariates Considered. The authors controlled for age in both comparisons, and sex in the comparison to the general population, but did not control for other key covariates including race/ethnicity, smoking, heavy alcohol intake, or genetic factors. They also did not control for other possible chemical exposures, despite describing other chemicals at the dry-cleaning facility. They also did not control for family history of PD despite 16% of participants in the tower and comparison group reporting a family history of PD. The amount of missing covariate data was not reported, which further limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from disease status data, but there was an insufficient consideration of latency (*i.e*., ≥ 1 year of employment at tower).

7.1.2 Case-Control Studies

I identified three case-control studies that examined the relationship between PCE exposure and PD incidence (Attachment F, Tables F.3 and F.4). Two of these studies examined this relationship in overlapping populations from the Finnish general population using occupational data reported on censuses that were linked to the FINJEM. Similar to the cohort studies on PCE and PD, none of the case-control studies assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Attachment C, Table C.1). Study summaries and additional quality issues in individual studies are described below and in Attachment C, Table C.1. Overall, because of these methodological limitations, these studies do not provide evidence for an association between PCE exposure and PD.

Goldman *et al*. (2012)

Overview

Goldman *et al*. (2012) examined risk of PD in 99 discordant male twin pairs from the NAS/NRC World War II Veteran Twins Cohort study. They did not report a statistically significant association between PD and any PCE exposure (OR = 10.5, 95% CI: 0.97-113), or a statistically significant increased risk with an increase in one tertile of PCE exposure-years (OR = 3.4, 95% CI: 0.9-12) or with an increase in one tertile of the cumulative exposure index (defined as the product of exposure intensity, hours exposed per year, and years exposed, summed across all jobs and hobbies) (OR = 9.3, 95% CI: 0.8-100).

Quality Considerations

Study Population. This discordant twin study appropriately selected and compared participants, but the results may not be generalizable to the general population. There was a high non-response rate (60-63%) in both cases and controls, and it is unknown how those who participated differed from those who did not. The overall sample size (99 pairs) and proportion of exposed participants (3-10%) were small, which is reflected in the low precision of the effect estimates.

Exposure Assessment. There was likely substantial exposure misclassification because of the indirect measurement of exposure based on self- or proxy- reported job and hobby histories. Also, while some analyses considered duration and cumulative exposure, other only assessed ever/never exposure. The proxy response rate was much greater for cases (46.5%) than controls (18.2%), which may have resulted in some information bias.

Outcome Assessment. All cases were likely captured, as this is a study of veterans, and cases were identified using VA, Health Care Financing Administration, NDI, and the NAS/NRC World War II Veteran Twins Cohort study records, and all were confirmed by a review of in-person evaluations, neurological exams, and medical records by two neurologists.

Covariates Considered. Because the participants were all male twins, age, sex, and race were the same among pairs. The authors controlled for respondent type (self or proxy) and smoking in the primary analysis, and certain solvent exposures (toluene, xylene, n-hexane, CCl_4, PCE) in secondary analyses. The authors did not consider or control for other solvent exposures or alcohol intake, which could have resulted in uncontrolled confounding. There were no missing covariate data, but variables were only considered at a single timepoint.

Temporality. There was an average of 38.3 years between first reported exposure and PD diagnosis. Information on exposures occurring decades prior was collected after the PD diagnoses, which could have resulted in recall or information bias. Only the sensitivity analyses considered latency (10-year lag).

Sallmén *et al*. (2023)

Overview

Sallmén *et al*. (2023) updated and expanded on a case-control study by Nielsen *et al*. (2021). This case nationwide Finnish case-control study included individuals who were between the 45 and 84 years of age between 1995 and 2014. The authors identified 17,187 incident PD and comparable movement disorder cases using prescription reimbursements registered under the Social Insurance Institution of Finland. A total of 35,738 controls were selected using incidence density sampling from the Population Information System register and matched on sex, birth year, and residency in Finland on index date. The authors reported no statistically significant associations between PD and increased PCE exposure (low IRR = 0.96, 95% CI: 0.82-1.13; medium IRR = 1.03, 95% CI: 0.83-1.28). The authors also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to a chemical-specific method results) and PBA that accounted for exposure measurement error. The results from the PBAs were attenuated, suggesting that the conventional analyses that did not account for exposure misclassification may have overestimated risks. PBAs were not conducted for PCE-specific exposures.

Quality Considerations

Study Population. These groups were appropriately selected, but the authors excluded approximately half of the potential sample population due to missing or incomplete census or occupational data. No information was provided on how those who were excluded differed from those who were not.

Exposure Assessment. The probability of exposure for individual cases and controls was estimated using FINJEM, which was linked to occupational information obtained from multiple national censuses (carried out every 5 years from 1970 to 2000 and annually from 2004 to 2008). Exposures may have been misclassified because they were based on job titles and no actual exposures were assessed. The duration and intensity of exposures was considered but time-variations in exposure (*e.g.*, daily or annual) were not considered. Only about 2% of participants were estimated to have any PCE exposure, which limited the precision of estimated effect estimates.

Outcome Assessment. The identification of cases through prescription reimbursements registered under the Social Insurance Institution of Finland is reliable and likely complete. The inclusion of comparable movement disorders limits the interpretation of the results, as grouping these outcomes with PD may be inappropriate if they have different underlying etiologies.

Covariates Considered. The authors adjusted for sex, birth year, and probability of smoking in primary analyses, and considered other chemical exposures (chromium, nickel, welding, polycyclic aromatic hydrocarbons, and aliphatic/alicyclic hydrocarbons or aromatic hydrocarbons) only in secondary analyses because the adjusted results differed by less than 10% from the unadjusted results. The authors did not control for or consider genetic factors or family history of PD or alcohol intake, which may have resulted in uncontrolled confounding. Covariates were only considered at a single timepoint, and the smoking variable was estimated based on surveys of Finnish residents linked to occupation and sex, which could have resulted in additional confounding or bias.

Temporality. Occupational histories were documented prior to the outcomes and an appropriate consideration of latency was included (≥ 5 years between exposure and outcome).

7.1.3 Conclusions

To date, only seven epidemiology studies in six unique populations have evaluated PCE exposure and PD, and the majority did not report statistically significant associations. All reported strong associations (*i.e.*, risk estimates > 2), including all of the positive statistically significant associations, had wide confidence intervals. All of these studies have methodological limitations that impact the interpretation of their results. Most notably, no studies provided direct measurements of individual-level PCE exposures, as drinking water studies do not consider whether or what amount of water individuals drank (or other potential drinking water exposures), and hobbies, job categories, or place of employment used in other studies may not be reliable surrogates for individuals' exposures to PCE. Because of these methodological limitations, I conclude that currently available epidemiology evidence does not support a causal association between PCE exposure and PD.

7.2 Toxicology

I reviewed US EPA (2011a, 2020a) and ATSDR (2017a, 2019a), and conducted a literature search using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). I did not identify any toxicity studies of PCE and PD.

7.3 Mode of Action

The metabolism of TCE and PCE yield some common metabolites, including TCA and minor metabolites of the glutathione conjugation pathway (US EPA, 2011a; Lock *et al*., 2013; Cichocki *et al*., 2016). According to Lock *et al*. (2013), "Assuming one of these common metabolites is responsible for the neuronal injury, then PCE may produce a similar effect in rodents to that of TCE." However, as discussed above in Section 5.3, there is no clear mechanism by which TCE may affect the dopaminergic system and there are considerable physiochemical, metabolic, and mechanistic differences between TCE and PCE, resulting in vastly different toxicological profiles (see Section 11.5.9). Available evidence does not support a MoA by which PCE could cause PD.

7.4 Agency Reviews

7.4.1 ATSDR

ATSDR (2017a) discussed the scientific evidence regarding PCE and PD in the Camp Lejeune review. This document cited the same epidemiology studies as it did for TCE, and stated, "The key study is the Goldman *et al*., 2012 twin study which found high elevations in risk for both PCE and TCE with evidence of an exposure-response relationship for exposure duration and cumulative exposure" (ATSDR, 2017a). However, as discussed in Section 6.1, Goldman *et al*. (2012) did not report any statistically significant associations with any exposure to PCE and CIs were extremely wide. This was true for increasing PCE exposure duration and with increasing cumulative exposure to PCE. This study also had a small number of PD cases, potential recall bias, and an unreliable exposure assessment.

ATSDR (2017a) also stated that "if a TCE metabolite is the cause of the damage, it is also possible that PCE could cause similar damage since TCE and PCE have some common metabolites (Lock *et al*., 2013)." However, ATSDR (2017a) concluded:

> For PCE, the epidemiological evidence is very limited and there is no available information on a plausible mechanism as there is for TCE. However, this may change if a metabolite of TCE that is common to PCE is found to be the agent causing damage to the dopaminergic neurons. Given what is presently known, ATSDR concludes that there is **below equipoise evidence for causation for PCE and Parkinson disease**. (emphasis in original)

In 2019, ATSDR published a Toxicological Profile for PCE (ATSDR, 2019b). It described the Goldman *et al*. (2012) and Bove *et al*. (2014a) epidemiology studies and concluded that "[a]dditional studies examining the potential relationship between [PCE] exposure and Parkinson's disease, especially studies with direct and quantitative measures of exposure, are needed before a conclusion can be drawn" (ATSDR, 2019b).

7.4.2 IOM

IOM reviewed the associations between solvent exposures and PD in the contexts of the Gulf War and Camp Lejeune. As discussed below, most of the studies included in IOM's review were not specific to PCE.

In an evaluation of insecticides and solvents in the context of the Gulf War, IOM (2003) determined that only Hertzman *et al*. (1994) and Seidler *et al*. (1996) were "sufficiently rigorous in design" to provide evidence on solvent exposure and PD. Both studies reported associations, but IOM (2003) concluded that "both studies were likely to have been subject to recall bias" and concluded "there [was] inadequate/insufficient evidence to determine whether an association exists between exposure to the solvents under review and Parkinson's disease."

In the assessment of potential health effects at Camp Lejeune, NRC (2009) identified three additional studies of solvent exposure and PD. McDonnell *et al*. (2003) conducted a case-control study of men in the United Kingdom; NRC (2009) stated that "[t]he study included a small number of cases and lacked information on other possible risk factors or confounders." Dick *et al*. (2007) was a case-control study conducted in five European countries that included 767 prevalent cases and 1,989 controls. NRC (2009) stated, "This study is characterized by a large number of subjects and provided no evidence of an association between solvent exposure and Parkinson disease." Finally, NRC (2009) included a cluster investigation of occupational exposure to TCE and PD or parkinsonism by Gash *et al*. (2008) and acknowledged "the significance of the study is difficult to judge" because of its design. NRC (2009) "conclude[d] that there continue[d] to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and Parkinson disease."

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 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 this review, the IOM committee identified four additional studies of solvent exposure and PD that had been published since the NRC (2009) report. This included the studies by Goldman *et al*. (2012) and Bove *et al*. (2014a,b), and the review by Lock *et al*. (2013). IOM (2015) stated:

> Despite the limitations of these studies, such as lack of statistical significance, the potential for recall bias, and the lack of incidence data pertaining to Parkinson's disease, the committee recommends including Parkinson's disease as an outcome associated with exposure to TCE and PCE. Because of the slow onset of Parkinson's disease, patients developing it years after their exposure, regardless of their age at exposure, may have not had symptoms at the time of exposure.

IOM (2015) acknowledged that "Lock *et al*. (2013) concluded that neither toxicologic nor epidemiologic studies present clear evidence that any specific solvent or class of solvents is an established cause of Parkinson's disease." Still, it concluded that PD is associated with PCE based on Goldman *et al*. (2012), Bove *et al*. (2014a,b), NRC (2009), and US EPA (2011a). However, the studies reviewed by NRC (2009) did not evaluate PCE specifically and, importantly, did not provide evidence of causation for any exposure to solvents and PD. The conclusions of IOM (2015) are not supported by the evidence as a whole, much less the studies on which IOM (2015) relied.

7.4.3 US EPA

In its Toxicological Review of PCE in 2012, US EPA (2012) stated, "Few studies are available on neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease and organic solvents (IOM, 2002), and none of these reports uniquely assess tetrachloroethylene." The agency provided no further discussion about the evidence regarding PCE exposure and PD.

US EPA (2020b) conducted its most recent review of PCE in 2020 and only summarized the Goldman *et al*. (2012) study in its evaluation. US EPA (2020b) noted that the association between self-reported ever exposure to PCE and PD reported from this study was "not statistically significant and highly unstable." The risk evaluation did not discuss this study further. US EPA (2020b) did not conclude that PCE is a known cause of PD.

7.4.4 Conclusions

IOM, ATSDR, and US EPA evaluated scientific studies of PCE and PD. None of these agencies has concluded that PCE is a known cause of PD (ATSDR, 2017a, 2019b; IOM, 2003, 2015; NRC, 2009; US EPA, 2012, 2020b).

7.5 Evidence Integration

A few epidemiology studies have evaluated PCE and PD. The small number of relevant epidemiology studies had higher quality outcome assessments and study designs, with limited evidence for selection bias and most accounted for temporality. Control for potential confounders varied across studies. No study, including those that assessed risks at Camp Lejeune, had adequate information on individual exposures, calling into question the reliability of reported risk estimates. Keeping these study strengths and limitations in mind, I evaluated the available epidemiology evidence as a whole in the context of Bradford Hill's considerations. I conclude that the evidence does not support a causal association between PCE and PD.

1. **Strength of Association.** There is no consistent evidence of strong associations, as risk estimates ranged from 0 to 10.5. Several risk estimates, including all > 2, were based on very low numbers of exposed cases (≤ 10) and had very wide CIs. These wide CIs lack precision and add uncertainty regarding the true magnitude of risk.
2. **Consistency.** While statistically significantly increased risk estimates were reported in two epidemiology studies of PCE exposures and PD, but statistically significant increased risks were not consistent within these studies, and one also reported a statistically significant decreased risk of PD in one analysis. Five other studies (some of overlapping populations, including Camp Lejeune) did not show consistent statistically significantly increased risk estimates. Risk estimates across all studies ranged widely, from 0 to 10.5.
3. **Specificity.** There is no evidence to suggest that there is a specific relationship between TCE and PD.
4. **Temporality.** Most of the epidemiology studies reviewed assessed exposure to TCE in a time period prior to disease occurrence (although indirectly). Further, while the exact relevant time window of exposure and latency period for PD is unknown, the periods of follow-up in the cohort studies were likely sufficient to account for temporality.
5. **Dose-Response.** Three studies evaluated PD risk with level of PCE exposure and none reported a consistent increased risk with increased exposure (Sallmén *et al*., 2023; ATSDR, 2018b; Goldman *et al*., 2012).
6. **Biological Plausibility.** No PCE toxicity studies have evaluated PD. It has been suggested that if TCE can cause PD *via* a metabolite that is also a PCE metabolite, then PCE could similarly cause PD. However, as discussed in Sections 5.4 and 10.5.9, there are considerable physiochemical, metabolic, and mechanistic differences between TCE and PCE, resulting in vastly different toxicological profiles. Also, experimental evidence does not support a causal relationship between

TCE exposure and PD in humans, even *via* a metabolite. Thus, there is no evidence that PCE is a biologically plausible cause of PD.

7. **Coherence.** Because of their methodological limitations and lack of consistency, epidemiology studies do not support an association between PCE exposure and PD. No PCE toxicity or MoA studies have evaluated PCE, and TCE toxicity and MoA studies do not support causation for TCE or a TCE metabolite that may be shared by PCE. The evidence is not coherent with respect to PCE and PD.
8. **Experiment.** There is no available experimental evidence in humans.
9. **Analogy.** It has been suggested that both TCE and PCE can produce TaClo, which may be analogous to MPTP in that they both can stimulate mitochondrial dysfunction, oxidative stress, and inflammation. However, to date, only one animal study has experimentally detected the endogenous formation of TaClo *in vivo* following subacute oral TCE (not PCE) exposure (Liu *et al*., 2018). In addition, the study evaluated oral exposure doses (250-1,000 mg/kg-day) that are much higher than typical human exposures, including at Camp Lejeune. No study has examined whether TaClo may be endogenously formed in humans following exposure to TCE or PCE *via* chronic ingestion or inhalation. Also, TCE was not found to lower dopamine levels in the SNpc in most studies. For these reasons, I conclude that, as a whole, the scientific evidence does not support the hypothesis that TCE or PCE can contribute to PD *via* the formation of TaClo.

7.6 Conclusions

No scientific or regulatory agency has concluded that PCE exposure is a known cause of PD. As a whole, epidemiology studies of PCE exposure do not provide evidence of an association with PD, as most analyses do not provide evidence of associations and all of the studies have methodological limitations that impact the interpretation of their results. PD has not been evaluated in PCE animal studies, and suggestions that a common metabolite of PCE and TCE may cause PD are not supported by the available evidence. Therefore, my opinion is that, as a whole, the currently available evidence does not support a causal association between PCE exposure and PD.

8 Benzene and PD

At room temperature, benzene is a colorless, transparent liquid with a sweet odor (ATSDR, 2007b; NTP, 1986). It has a relatively high vapor pressure of 94.8 millimeters of mercury (mmHg) at 25°C (IARC, 2018). In the natural environment, benzene is emitted from volcanoes and forest fires and is present in crude oil. Benzene has been widely applied in various industrial processes and as an additive to unleaded gasoline (IARC, 2018). Common anthropogenic sources of benzene exposure include tobacco smoke, automobile service stations, exhaust from motor vehicles, and industrial emissions (ATSDR, 2007b). Automobile exhaust is the largest source of benzene in the environment (WHO, 2010). 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 (IARC, 2018; ATSDR, 2007b).

No epidemiology or animal studies have evaluated benzene exposure alone and PD. No scientific or regulatory agency has addressed whether benzene is a known cause of PD. The scientific evidence regarding benzene exposure and PD is discussed below.

8.1 Epidemiology

I reviewed the studies considered by US EPA (2002) and ATSDR (2007b, 2015, 2017a) and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). I identified two Camp Lejeune cohort studies and three case-control studies of overlapping populations that examined the association between benzene and PD (Attachment G, Tables G.1-G.4). I review here both Camp Lejeune studies that evaluated benzene-specific exposures, for completeness, and the more recent of the two case-control studies with overlapping populations. No epidemiology study directly evaluated the association between benzene exposure and PD. Both cohort studies estimated benzene indirectly based on modeled exposures in drinking water at Camp Lejeune (other Camp Lejeune studies did not evaluate benzene specifically). None of these studies had information on whether or what amount of water individuals drank or other drinking water exposures. In addition, none of the studies controlled for other potential chemical exposures.

I summarize the characteristics, results, and quality of the epidemiology studies related to benzene and PD below and in Attachment G, Tables G.1-G.4, and Attachment C, Table C.1. Overall, primarily because of a lack of consistent associations and methodological limitations, these studies do not provide evidence for a causal association between benzene exposure and PD.

8.1.1 Cohort Studies

I identified two cohort studies that evaluated benzene exposure and PD, both of which were conducted in US Marines and Navy personnel at Camp Lejeune or civilian workers potentially exposed to benzene *via* contaminated water. I discuss these studies in detail in Section 5. These studies included overlapping populations (mortality: ATSDR [2018b]; Bove *et al*. [2014a]; incidence: ATDSR [2018b]). Neither study assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Attachment C, Table C.1). Individuals were considered exposed if they lived or worked on base in some analyses, while exposure estimates in other analyses were based on the estimated monthly average benzene concentration in groundwater while study participants lived or worked there. There was no information on

water consumption or actual individual exposures to benzene or other chemicals in drinking water. Additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between benzene exposure and PD.

Bove *et al*. (2014a)

Overview

Bove *et al*. (2014a) retrospectively evaluated PD deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985, and who had been potentially exposed to benzene-contaminated drinking water on base. Between 1979 and 2008, there were five PD deaths in the cohort. There was no increased risk of PD mortality within the cohort when the authors compared those with estimated cumulative exposures to benzene greater than the median to those with less than the median (HR = 2.52, 95% CI: 0.20-31.59). The authors reported similar results in models of $\log_{10}$ continuous cumulative benzene exposure.

Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 2%), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the study, less than 15% of the study population had died, and only a small number of PD deaths were observed (n = 5), which limits precision of the estimated associations.

Exposure Assessment. Potential exposures were estimated based on groundwater fate and transport models of the monthly average concentrations of benzene in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. These benzene-specific estimates are more reliable than exposure estimates that are not based on any quantitative information (*e.g*., any employment on base), but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely.

Outcome Assessment. The study assessed PD mortality, which is weaker than examining PD incidence, because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e*., SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for sex and occupation (blue *vs.* white collar). The authors considered but did not control for age because the adjusted results differed from the unadjusted results by less than 10%. The authors did not consider or control for genetic factors, family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly to use as a proxy for other potential occupational exposures, it is unclear if they

analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

ATSDR (2018b)

Overview

In a population that overlapped with the one analyzed by Bove *et al*. (2014a), ATSDR (2018b) conducted a health survey from 2011 to 2012 that collected information on PD and lifestyle and demographic factors from 50,684 Marines and Navy personnel and 2,168 civilian employees stationed or employed at Camp Lejeune between 1972 and 1985. The authors compared PD incidence in Camp Lejeune to incidence in 8,615 Marines and Navy personnel or 1,425 civilian employees at Camp Pendleton. They also compared PD incidence by levels of exposure to benzene within the Camp Lejeune cohort. The authors reported no associations between PD and any level of cumulative exposure to benzene in Marines and Navy personnel stationed at Camp Lejeune compared to those at Camp Pendleton (low exposure OR = 0.86, 95% CI: 0.47-1.59; medium exposure OR = 0.87, 95% CI: 0.46-1.62; high exposure OR = 0.29, 95% CI: 0.08-1.00). There were no increased risks reported when medium or high cumulative exposures at Camp Lejeune were compared to low exposures.

Quality Considerations

Study Population. This study used appropriate comparison groups, but selection bias is likely. 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 authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

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

Exposure Assessment. Exposures to benzene were estimated based on groundwater fate and transport and water distribution system models coupled with historical occupation codes, period and duration of employment or residence, and workplace or residence location. These benzene-specific exposures are more reliable than exposure estimates that are not based on any quantitative information (*e.g.*, assignment on base), but without a direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption/exposure data), it is still likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures 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 exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Finally, there was a high correlation between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs in the ATSDR (2018b) study, which limits the interpretation of chemical-specific results.

In a deposition, Dr. Bove (2024a) states, "The Marine Corps…didn't know, where barracks were on base, where units were barracked on base. And we relied on CAP [community assistance panel] members plus people they knew who had that memory…" Dr. Bove (2024a) also stated that they were not able to take into account a Marine's deployment off base and so they assumed that the DMDC data represented a continuous presence at Camp Lejeune, raising more concerns over 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al*., 1991) or multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed that nondifferential exposure measurement error could lead to bias towards or away from the null in a recent deposition, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

Outcome Assessment. Cases were confirmed using medical records or death certificates, but initial reliance on self-reported cases could have resulted in some missed cases. There were a small number of PD cases in the civilian population (n = 20), which may have resulted in reduced precision. This analysis also focused on PD incidence, which is more informative than analyses evaluating mortality, since PD is not a fatal disease.

Covariates Considered. The authors only controlled for sex in their analyses. They considered but did not control for age, smoking, alcohol, or other potential occupational exposures or chemical exposures because adjusted results differed from unadjusted results by less than 10%. The authors did not consider or control for genetic factors or family history of PD. Covariate data were collected at a single timepoint *via* self-report and smoking, alcohol consumption, and other occupational exposures were missing for more than 5% of participants, increasing the likelihood of biased results.

Temporality. The study exposure and outcome periods overlapped, with follow-up beginning coincident with first exposure (*i.e.,* exposures could continue to occur after follow-up began). Some participants were followed for up to 40 years, but the authors did not consider a latency period.

8.1.2 Case-Control Studies

I identified three case-control studies examining the relationship between benzene exposure and PD incidence (Attachment G, Tables G.3 and G.4). Two of these studies examined this relationship in overlapping populations from the Finnish general population using occupational data reported on censuses that were linked to the FINJEM. Similar to the cohort studies on benzene and PD, none of the case-control studies assessed exposure in a manner that was sensitive or specific enough to be considered higher quality (Attachment C, Table C.1). Study summaries and additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between benzene exposure and PD.

Park *et al*. (2005)

Overview

Park *et al*. (2005) conducted a US-based case-control study to examine associations between occupational groups and PD mortality. The authors identified 33,678 PD deaths from death certificates from 22 states between 1992 and 1998 using the National Occupational Mortality Surveillance System. There were 2,501,541 controls who were all decedents with no mention of neurologic disease. Decedent occupation, business or industry type, and demographic information (*i.e*., age, race, gender, region, and SES) were obtained from the 1980 US Census Bureau system. The authors reported no statistically significant association between benzene exposure and PD mortality (OR = 1.05, 95% CI: 0.98-1.12).

Quality Considerations

Study Population. This study used appropriate comparison groups. The authors excluded individuals that had "housekeeper" as their designated occupation or that had missing occupation information, but did not say how many people were excluded.

Exposure Assessment. Exposure to benzene was assessed using a JEM that was previously validated for cancer studies. Occupational data were self-reported at a single time point, which may have resulted in information bias, and there was no assessment of actual exposures, so exposure misclassification was likely.

Outcome Assessment. The use of PD mortality data was not a good surrogate for incidence, because PD is not a fatal disease.

Covariates Considered. The authors controlled for age and sex but did not consider or control for genetic factors, family history of PD, alcohol consumption, smoking, or other chemical exposures, which could have resulted in uncontrolled confounding.

Temporality. Occupational data were collected prior to the outcome, but the authors did not consider any latency period between exposure and outcome.

Sallmén *et al*. (2023)

Overview

Sallmén *et al*. (2023) updated and expanded on a case-control study by Nielsen *et al*. (2021). This case nationwide Finnish case-control study included individuals who were between the 45 and 84 years of age between 1995 and 2014. The authors identified 17,187 incident PD and comparable movement disorder cases using prescription reimbursements registered under the Social Insurance Institution of Finland. A total of 35,738 controls were selected using incidence density sampling from the Population Information System register and matched on sex, birth year, and residency in Finland on index date. The authors reported no statistically significant associations between PD and increased benzene exposure (low IRR = 1.02, 95% CI: 0.95-1.11; high IRR = 1.03, 95% CI: 0.90-1.18). The authors also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to a chemical-specific method results) and PBA that accounted for exposure measurement error. The results from the PBAs were attenuated, suggesting that the conventional analyses that did not account for exposure misclassification may have overestimated risks. PBAs were not run for benzene-specific exposures.

Quality Considerations

Study Population. These groups were appropriately selected, but the authors excluded approximately half of the potential sample population due to missing or incomplete census or occupational data. No information was provided on how those who were excluded differed from those who were not.

Exposure Assessment. The probability of exposure for individual cases and controls was estimated using FINJEM, which was linked to occupational information obtained from multiple national censuses (carried out every 5 years from 1970 to 2000 and annually from 2004 to 2008). Exposures may have been misclassified because they were based on job titles and no actual exposures were assessed. The duration and intensity of exposures was considered but time-variations in exposure (*e.g*., daily or annual) were not considered. Only about 8% of participants were estimated to have any benzene exposure, which limited the precision of estimated effect estimates.

Outcome Assessment. The identification of cases through prescription reimbursements registered under the Social Insurance Institution of Finland is reliable and likely complete. The inclusion of comparable movement disorders limits the interpretation of the results, as grouping these outcomes with PD may be inappropriate if they have different underlying etiologies.

Covariates Considered. The authors adjusted for sex, birth year, and probability of smoking in primary analyses, and considered other chemical exposures (chromium, nickel, welding, polycyclic aromatic hydrocarbons, and aliphatic/alicyclic hydrocarbons or aromatic hydrocarbons) only in secondary analyses because the adjusted results differed by less than 10% from the unadjusted results. The authors did not control for or consider genetic factors or family history of PD or alcohol intake, which may have resulted in uncontrolled confounding. Covariates were only considered at a single timepoint, and the smoking variable was estimated based on surveys of Finnish residents linked to occupation and sex, which could have resulted in additional confounding or bias.

Temporality. Occupational histories were documented prior to the outcomes and an appropriate consideration of latency was included (≥ 5 years between exposure and outcome).

8.1.3 Conclusions

To date, only five epidemiology studies in four unique populations have evaluated benzene exposure and PD, and none reported any statistically significant associations. All of these studies have methodological limitations that impact the interpretation of their results. Most notably, no studies provided direct measurements of individual-level benzene exposures, as drinking water studies do not consider whether or what amount of water individuals drank or other drinking water exposures, and hobbies, job categories, or employment location used in other studies may not be reliable surrogates for individuals' exposures to benzene. Because of these methodological limitations, I conclude that epidemiology evidence does not support a causal association between benzene exposure and PD.

8.2 Toxicology

I reviewed US EPA (2002) and ATSDR (2007b, 2015, 2017a) and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). None of the toxicity studies I identified examined benzene exposure and PD.

8.3 Mode of Action

No MoAs for benzene exposure and PD have been investigated.

8.4 Agency Reviews

In assessments of potential health effects at Camp Lejeune, NRC (2009) and IOM (2015) concentrated on "the primary solvents found in the drinking water at Camp Lejeune – TCE and PCE" (IOM, 2015). IOM (2015) noted that "[a]lthough contaminants other than TCE and PCE – such as benzene, toluene, and vinyl chloride – were present in the drinking water at Camp Lejeune, they were generally found at very low concentrations and not in all samples." IOM (2015) also mentioned that in Bove *et al*. (2014a), "[f]our of the five Camp Lejeune cases were associated with a cumulative exposure above the median for TCE and PCE as well as for vinyl chloride and benzene resulting in hazard ratios of greater than 2.50 ($p \leq 0.05$)," but did not discuss whether any of these chemicals were likely to have contributed to PD in these individuals. There is no further discussion of benzene.

PD is not discussed in the 2007 ATSDR "Toxicological Profile for Benzene" (ATSDR, 2007b) or the "Toxicological Profile for Benzene (Draft for Public Comment)" (ATSDR, 2024a). Similarly, in a review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) did not evaluate benzene exposure and PD. US EPA (2002) also did not mention PD in its "Toxicological Review of Benzene (Noncancer Effects) (CAS No. 71-43-2)."

8.5 Evidence Integration

Few epidemiology studies have evaluated benzene and PD. The small number of relevant epidemiology studies had higher quality outcome assessments and study designs, with limited evidence for selection bias and most accounted for temporality. Control for potential confounders varied across studies. No study, including those that assessed risks at Camp Lejeune, had adequate information on individual exposures, calling into question the reliability of reported risk estimates. Keeping these study strengths and limitations in mind, I evaluated the available epidemiology evidence as a whole in the context of Bradford Hill's

considerations. I conclude that the evidence does not support a causal association between benzene and PD.

1. **Strength of Association.** There is no consistent evidence of strong associations between benzene exposure and PD, as most risk estimates were close to 1 or less than 1, ranging from 0.33 to 2.52. The only risk estimates > 1.05 was based on only four exposed cases and had a very wide CI indicating a lack precision and add uncertainty regarding the true magnitude of risk in that study.
2. **Consistency.** None of the studies reported statistically significantly increased risk estimates. Risk estimates ranged widely, from 0.33 to 2.52, but most were close to or less than 1.
3. **Specificity.** There is no evidence to suggest that there is a specific relationship between benzene and PD.
4. **Temporality.** Most epidemiology studies assessed exposure to benzene in a time period prior to disease occurrence (although indirectly). Further, while the exact relevant time window of exposure and latency period for PD is unknown, the periods of follow-up in the cohort studies were likely sufficient to account for temporality.
5. **Dose-Response.** Two studies evaluated PD risk with level of benzene exposure (Sallmén *et al*., 2023; ATSDR, 2018b). Neither study reported an increased risk with any level of exposure and all risk estimates were ≤ 1.03. Neither study reported a p-trend. Notably, in ATSDR (2018b) benzene was correlated with TCE, vinyl chloride, and TVOCs, so these analyses were not specific to benzene.
6. **Biological Plausibility.** There is no available evidence that indicates that it is biologically plausible that benzene can cause PD.
7. **Coherence.** Because of their methodological limitations and lack of consistency, epidemiology studies do not support an association between benzene and PD. There is no experimental evidence available to judge coherence.
8. **Experiment.** There is no available experimental evidence in humans.
9. **Analogy.** There are no available analogies.

8.6 Conclusions

No scientific or regulatory agency has concluded that benzene exposure is a known cause of PD. The few epidemiology studies that evaluated benzene exposure do not provide evidence of an association with PD, as they reported null results with point estimates mostly below or close to 1 and have methodological limitations that impact the interpretation of their results. PD has not been evaluated in benzene animal studies. Therefore, I conclude that, as a whole, the currently available evidence does not support a causal association between benzene exposure and PD.

9 Vinyl Chloride and PD

Vinyl chloride is a colorless, flammable gas with a mild, sweet odor that is not stable 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 PVC, which is used to make plastic products like pipes, wire and cable coatings, and packaging materials (ATSDR, 2023a).

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 (ATSDR, 2023a).

No epidemiology or animal studies have evaluated vinyl chloride exposure alone and PD. No scientific or regulatory agency has addressed whether vinyl chloride is a known cause of PD. The scientific evidence regarding vinyl chloride exposure and PD is discussed below.

9.1 Epidemiology

I reviewed the studies considered by US EPA (2000a,b) and ATSDR (2006, 2016, 2017a) and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). No epidemiology study has directly evaluated the association between vinyl chloride exposure and PD. The few studies that evaluated vinyl chloride indirectly each evaluated overlapping populations of Marines and Navy personnel stationed at or civilians working at Camp Lejeune when drinking water was contaminated with vinyl chloride (Attachment H, Tables H.1-H.2). None of these studies had information on whether or what amount of water individuals drank or were exposed to on base. In addition, none of the studies controlled for other potential chemical exposures. Because of these methodological limitations, I conclude that the currently available epidemiology evidence does not support a causal association between vinyl chloride exposure and PD.

9.1.1 Cohort Studies

I identified two cohort studies that evaluated the relationship between vinyl chloride exposure and PD, both of which were conducted in populations at Camp Lejeune, one in US Marines and Navy personnel and the other in civilians potentially exposed to vinyl chloride *via* contaminated water (mortality: ATSDR [2018b]; Bove *et al*. [2014a]; incidence: ATDSR [2018b]) (Attachment H, Tables H.1-H.2). I do not discuss other Camp Lejeune studies because they did not evaluate vinyl chloride-specific exposures (*e.g*., exposure was assumed if a person was stationed at Camp Lejeune). Neither of these studies assessed exposure in a manner that can be considered high quality (Attachment C, Table C.1). Individuals were considered exposed based on the estimated monthly average vinyl chloride concentration in drinking water while they lived or worked on base. There was no information on water consumption or actual individual exposures to vinyl chloride or other chemicals in drinking water. Additional quality issues in individual studies are described below. Overall, because of these methodological limitations, these studies do not provide evidence for an association between vinyl chloride exposure and PD.

Bove *et al*. (2014a)

Overview

Bove *et al*. (2014a) retrospectively evaluated PD deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985, and who had been potentially exposed to vinyl chloride-contaminated drinking water on base. Between 1979 and 2008, there were five PD deaths in the cohort. There was no increased risk of PD mortality when comparing those with estimated cumulative exposures to vinyl chloride greater than the median to those with estimated cumulative exposures less than the median (HR = 2.81, 95% CI: 0.23-34.11). The authors reported similar results in models with $\log_{10}$ continuous cumulative vinyl chloride exposure.

Quality Considerations

Study Population. This study had no obvious risk of selection bias, had low loss to follow-up (< 2%), and used appropriate comparison groups. Most of the cohort was younger than 65 years of age at the end of the study, less than 15% of the study population had died, and only a small number of PD deaths were observed (n = 5), which limits precision of the estimated associations.

Exposure Assessment. Potential exposures were estimated based on groundwater fate and transport models of the monthly average concentrations of vinyl chloride in the water distribution system that supplied most of the civilian workplace locations. Workers were considered exposed to the modeled monthly average water concentration for every month they were employed. The vinyl chloride-specific estimates are more reliable than exposure estimates that are not based on any quantitative information (*e.g*., any employment on base), but without a direct link to information on individual-level water consumption/exposures, they are likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures based on chemical concentrations in the groundwater supplying different locations on base depends on the accuracy of the model's assumptions, and while the time-varying nature of the exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-term or even average exposure concentrations. Therefore, exposure misclassification is likely.

Outcome Assessment. The study assessed PD mortality, which is weaker than examining PD incidence, because PD is not a fatal disease. Reliable sources were used to identify deaths (*i.e*., SSA, commercial tracing service, NDI).

Covariates Considered. The authors controlled for sex and occupation (blue *vs.* white collar). The authors considered but did not control for age because the adjusted results differed from the unadjusted results by less than 10%. The authors did not consider or control for genetic factors, family history of PD, alcohol intake, or smoking in any analyses, which could have resulted in uncontrolled confounding. Bove (2024a) stated, "Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC." Therefore, it is unlikely that co-exposures were fully controlled in the model, and residual confounding is likely. In addition, while the authors collected occupational data quarterly to use as a proxy for other potential occupational exposures, it is unclear if they analyzed those data in a time-varying manner, and the amount of missing covariate data was not reported, which limits the ability to fully interpret the results.

Temporality. Employment histories were collected separately from outcome data and an appropriate latency period was considered (*e.g.*, 10-year lag).

ATSDR (2018b)

Overview

In a population that overlapped with the one analyzed by Bove *et al.* (2014a), ATSDR (2018b) conducted a health survey from 2011 to 2012 that collected information on PD and lifestyle and demographic factors from 50,684 Marines and Navy personnel stationed at Camp Lejeune and 2,168 civilian employees employed at Camp Lejeune between 1972 and 1985. The authors compared PD incidence in Camp Lejeune to incidence in 8,615 Marines and Navy personnel or 1,425 civilian employees at Camp Pendleton. There was no association between PD and any level of cumulative vinyl chloride exposure in Marines and Navy personnel stationed at Camp Lejeune compared to Camp Pendleton (low exposure OR = 0.86, 95% CI: 0.47-1.59; medium exposure OR = 0.87, 95% CI: 0.46-1.62; high exposure OR = 0.29, 95% CI: 0.87-8.94). There were no increased risks reported when medium or high cumulative exposures at Camp Lejeune were compared to low exposures at Camp Lejeune.

Quality Considerations

Study Population. This study used appropriate comparison groups, but selection bias is likely. 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 authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

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

Exposure Assessment. Exposures to vinyl chloride were estimated based on groundwater fate and transport and water distribution system models coupled with historical occupation codes, period and duration of employment or residence, and workplace or residence location.

These direct measurements are more reliable than exposure estimates that are not based on any quantitative information (*e.g.*, assignment on base), but without a direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption/exposure data), it is still likely to be inaccurate with respect to individual exposures. Further, the modeling of individual exposures 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 exposures were considered in the model, they are limited by the timing and frequency of measurements and do not necessarily reflect long-

term or even average exposure concentrations. Finally, there was a high correlation between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs in the ATSDR (2018b) which limits the interpretation of the vinyl chloride-specific results.

In a deposition, Dr. Bove (2024a) states, "The Marine Corps…didn't know, where barracks were on base, where units were barracked on base. And we relied on CAP [community assistance panel] members plus people they knew who had that memory…" Dr. Bove (2024a) also stated that they were not able to take into account a Marine's deployment off base and so they assumed that the DMDC data represented a continuous presence at Camp Lejeune, raising more concerns over 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al*., 1991) or multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed that nondifferential exposure measurement error could lead to bias towards or away from the null in a recent deposition, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

Outcome Assessment. Cases were confirmed using medical records or death certificates, but initial reliance on self-reported cases could have resulted in some missed cases. There were a small number of PD cases in the civilian population (n = 20), which may have resulted in risk estimates with reduced precision. This analysis focused on PD incidence, which is more informative than analyses evaluating mortality, since PD is not a fatal disease.

Covariates Considered. The authors only controlled for sex in their analyses. They considered but did not control for age, smoking, alcohol, or other potential occupational exposures or chemical exposures because adjusted results differed from unadjusted results by less than 10%. The authors did not consider or control for genetic factors or family history of PD. Covariate data were collected at a single timepoint *via* self-report and smoking, alcohol consumption, and other occupational exposures were missing for more than 5% of participants, increasing the likelihood of biased results.

Temporality. The study exposure and outcome periods overlapped, with follow-up beginning coincident with first exposure (*i.e.,* exposures could continue to occur after follow-up began). Some participants were followed for up to 40 years, but the authors did not consider a latency period.

9.1.2 Conclusions

To date, only two epidemiology studies in populations at Camp Lejeune have evaluated vinyl chloride exposure and PD, and neither report statistically significant associations. Both of these studies evaluated vinyl chloride indirectly in Marines and Navy personnel stationed at Camp Lejeune or civilians working at Camp Lejeune when drinking water was contaminated with vinyl chloride. Both of these studies have methodological limitations that impact the interpretation of their results. Most notably, neither study provided direct measurements of individual-level vinyl chloride exposures, as they did not consider whether or what amount of water individuals drank on base. Because of these methodological limitations, I conclude that currently available epidemiology evidence does not support a causal association between vinyl chloride exposure and PD.

9.2 Toxicology

I reviewed US EPA (2000a,b) and ATSDR (2006, 2016, 2017a), and conducted literature searches using PubMed and Scopus for any relevant studies published after the cut-off dates in these reports (Attachment A). None of the toxicity studies I identified examined vinyl chloride exposure and PD.

9.3 Mode of Action

No MoAs for vinyl chloride exposure and PD have been investigated.

9.4 Agency Reviews

In assessments of potential health effects at Camp Lejeune, NRC (2009) and IOM (2015) concentrated on "the primary solvents found in the drinking water at Camp Lejeune – TCE and PCE" (IOM, 2015). IOM (2015) noted that "[a]lthough contaminants other than TCE and PCE – such as benzene, toluene, and vinyl chloride – were present in the drinking water at Camp Lejeune, they were generally found at very low concentrations and not in all samples." IOM (2015) also mentioned that in Bove *et al*. (2014a), "[f]our of the five Camp Lejeune cases were associated with a cumulative exposure above the median for TCE and PCE as well as for vinyl chloride and benzene resulting in hazard ratios of greater than 2.50 ($p \leq 0.05$)," but did not discuss whether any of these chemicals were likely to have contributed to PD in these individuals. There is no further discussion of vinyl chloride.

In a review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) did not evaluate vinyl chloride and PD. In the ATSDR (2023a) "Toxicological Profile for Vinyl Chloride" and the US EPA (2000a) "Toxicological Review of Vinyl Chloride (CAS No. 75-01-4)," PD is not discussed.

9.5 Evidence Integration

Two cohort studies evaluated the relationship between vinyl chloride exposure and PD, both of which were conducted in populations at Camp Lejeune potentially exposed *via* contaminated water. The small number of relevant epidemiology studies generally accounted for temporality, and had higher quality outcome assessments and study designs, with limited evidence for selection bias. Control for potential confounders varied. Neither study had adequate information on individual exposures, calling into question the reliability of reported risk estimates. Keeping these study strengths and limitations in mind, I evaluated the available

epidemiology evidence as a whole in the context of Bradford Hill's considerations. I conclude that the evidence does not support a causal association between vinyl chloride and PD.

1. **Strength of Association.** There is no consistent evidence of strong associations between vinyl chloride exposure and PD. Risk estimates ranged from 0.33 to 2.81; but most were ≤ 1. Several estimates were based on very low numbers of exposed cases and had very wide CIs. These wide CIs lack precision and add uncertainty regarding the true magnitude of risk.
2. **Consistency.** One study reported a single risk estimate > 1, while the other study reported several risk estimates which were all ≤ 1. Neither study reported any statistically significant associations.
3. **Specificity.** There is no evidence to suggest that there is a specific relationship between vinyl chloride and PD.
4. **Temporality.** One study exposure to vinyl chloride in a time period prior to disease occurrence (although indirectly) while the exposure and follow-up periods had the potential to overlap in the other study. However, while the exact relevant time window of exposure and latency period for PD is unknown, the periods of follow-up in both studies were likely sufficient to account for temporality.
5. **Dose-Response.** Only ATSDR (2018b) examined PD risk levels of vinyl chloride exposure. This study reported no increased risk of PD with any level of exposure (all risk estimates were ≤ 1) in Marines and Navy personnel. Vinyl chloride was correlated with TCE, benzene, and TVOCs, so analyses were not specific to vinyl chloride.
6. **Biological Plausibility.** There is no available evidence that indicates that it is biologically plausible that vinyl chloride can cause PD.
7. **Coherence.** Because of their methodological limitations and lack of consistency, epidemiology studies do not support an association between vinyl chloride exposure and PD. There is no experimental evidence available to judge coherence.
8. **Experiment.** There is no available experimental evidence in humans.
9. **Analogy.** There are no available analogies.

9.6 Conclusions

No scientific or regulatory agency has concluded that vinyl chloride exposure is a known cause of PD. The two epidemiology studies that evaluated vinyl chloride exposure and PD do not provide evidence for an association, as they reported inconsistent results, with risk estimates mostly ≤ 1, and have methodological limitations, particularly exposure misclassification and co-exposures that were not fully accounted for, that impact the interpretation of their results. None of the vinyl chloride toxicity studies I identified examined PD. Therefore, I conclude that, as a whole, the currently available evidence does not support a causal association between vinyl exposure and PD.

10 *trans*-1,2-DCE and PD

In this section, I discuss studies that assessed *trans*-1,2-DCE exposure and PD, 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 PD.

I did not identify any epidemiology studies that investigated *trans*-1,2-DCE exposure and the risk of PD. 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 TVOCs combined on base (see Section 5), but none specifically evaluated risks associated with *trans*-1,2-DCE. As such, they do not provide information with respect to *trans*-1,2-DCE.

I did not identify any chronic *trans*-1,2-DCE animal toxicity studies. NTP (2002) exposed F344/N rats and B6C3F1 mice to *trans*-1,2-DCE in feed for 14 weeks at doses ranging from 3,125 to 50,000 ppm. NTP (2002) did not evaluate endpoints related to PD. To my knowledge, ATSDR's draft "Toxicological Profile for 1,2-Dichloroethene" is the only agency review of 1,2-DCE. ATSDR (2023b) did not discuss PD.

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

11 Review of Plaintiffs' Expert Opinions

While I was asked to opine on whether chemicals in Camp Lejeune water could have caused PD in exposed individuals, seven Plaintiffs' experts – Dr. Steven B. Bird (2024), Dr. Amelia K. Boehme (2024), Dr. Jason Cannon (2024), Dr. Lucio G. Costa (2024), Dr. Briana R. De Miranda (2024), Dr. Michael D. Freeman (2024), and Dr. Gary W. Miller (2024) – based their opinions on classification categories used for regulatory purposes that are based on certain presumptions. All of these experts opine on TCE and PD risk. All but Dr. De Miranda opine on PCE, and Dr. Bird and Dr. Freeman discuss benzene and vinyl chloride and PD risk. Their opinions are not all consistent, and some are contradictory (Table 11.1). All conclude that TCE is either causal or at least as likely as not to cause PD generally or at Camp Lejeune. The experts mostly conclude that PCE was at least as likely as not to cause Parkinson's generally or at Camp Lejeune, although Dr. Costa acknowledges there was less evidence for PCE than for TCE, and Dr. De Miranda does not provide a conclusion on PCE, but indicates it is possible PCE can contribute to PD. Dr. Bird concludes that both benzene and vinyl chloride are at least as likely as not causes of PD, while Dr. Freeman concludes the evidence is below equipoise for benzene and vinyl chloride. No other expert opines on benzene or vinyl chloride independently, Dr. Boehme stated that evidence is supportive for solvents or VOCs more generally.

Table 11.1 Plaintiffs' Experts' PD Causal Conclusions

Expert	TCE	PCE	Benzene	Vinyl Chloride	Other VOCs
Dr. Bird (2024)	As/more likely as not at CL	As/more likely as not at CL	As/more likely as not at CL	As/more likely as not at CL	-
Dr. Boehme (2024)	More likely than not at CL	More likely than not at CL	-	-	More likely at CL
Dr. Cannon (2024)	Causal	At least as likely as not	-	-	-
Dr. Costa (2024)	At least as likely or not	Less evidence, but causal link	-	-	-
Dr. De Miranda (2024)	More likely than not at CL	-	-	-	-
Dr. Freeman (2024)	Sufficient	Equipoise and above	Below equipoise	Below equipoise	-
Dr. Miller (2024)	More likely than not at CL	At least as likely as not at CL	-	-	-

Notes:
CL = Camp Lejeune; PCE = Perchloroethylene; PD = Parkinson's Disease; TCE = Trichloroethylene; VOC = Volatile Organic Compound.

Several Plaintiffs' experts rely on the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) as a basis for their opinions. Major issues with this assessment are discussed Section 11.1. Section 11.2 notes how Plaintiffs' experts do not provide scientific support for their conclusion that most causes of PD are environmental. I discuss issues with the Plaintiffs' experts' evaluations of epidemiology evidence in Section 11.3. This includes a discussion of how they identified and selected studies, evaluate study quality, interpret statistical significance, and calculate a population attributable fraction (PAF), in addition to their reviews of Goldman *et al*. (2012) and Camp Lejeune epidemiology studies, and other epidemiology studies. In Section 11.4, I discuss the Plaintiffs' experts' reviews of experimental evidence, including how they identified and selected studies, evaluate MoA, consider the relevance of high doses, interpret dose-response

and inconsistent study results, and consider systemic toxicity and the relevance of animal models to humans. In Section 11.5, I evaluate their Bradford Hill assessments of the evidence, followed by a review of their opinions on exposures, benzene, vinyl chloride, and mixtures in Sections 11.6 to 11.9. In Section 11.10, I review Dr. Canon's discussion and interpretation of US EPA's 2024 TCE and PCE rulings (US EPA 2024a,b). As discussed in detail below, the Plaintiffs' experts' evaluations do not demonstrate that one can conclude to a degree of scientific certainty that TCE, PCE, benzene, or vinyl chloride in Camp Lejeune drinking water can cause PD.

11.1 ATSDR Assessment of the Evidence

ATSDR (2017a) does not conclude that evidence for PD causation is equipoise or above for PCE, benzene, or vinyl chloride. Its conclusion that evidence is equipoise and above for TCE is not supported by an objective, systematic review.

Several experts rely on the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) as a basis for their opinions, without critically evaluating this assessment. ATSDR (2017a) stated, "The purpose [of this assessment] 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 assessment represents ATSDR's assessment of the state of evidence at this time." This assessment did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation. Conclusions regarding causation for many health outcomes, including PD, are inconsistent with those of several other agency reviews.

In his recent deposition, Dr. Bove (2024a) indicated that he was the sole author of this assessment. 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 then generally undergo a rigorous peer-review process. In his deposition, Bove (2024a) acknowledged that this type of review was unusual to conduct at ATSDR. 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) and can involve a dozen authors and three peer-reviewers. The instructions for peer reviewers demonstrate how comprehensive the evaluations are (ATSDR, 2024b). ATSDR also considers public comments on draft Toxicological Profiles. The process can take years. It is clear that the review conducted by ATSDR (2017a) is not of the caliber of reviews generally conducted by ATSDR.

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.

More specifically, the assessment 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 assessment 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 CIR cutoffs were or why they were not the same. I am not aware of any epidemiology textbooks or peer-reviewed environmental epidemiology studies that use this metric.

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. A noted in Section 3.1.1 of this report, 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 protection; there would be very 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 when statistical significance isn't achieved, even though it's based on the same statistics

It is also critical to understand that p-values, CIs, and CIRs are only informative with respect to random error. If a study sample is not representative of the underlying population one wishes to make inferences about or if there is bias or confounding, statistical significance is moot. This is illustrated by Savtiz (2024). In his discussion of a CIR = 3, he states:

> I think it's how informative it is in terms of random error, in other words, it's only one consideration. There could still be the presence or absence of confounding or dose-response gradients or all these other factors we talk about, but zeroing in on the issue of precision, it's a way to convey a sense of how informative it is in a statistical sense.

Also, ATSDR (2017) concluded a number of health conditions are causally associated with TCE, PCE, benzene, and vinyl chloride. Every chemical has some degree of specificity with respect to health conditions it can cause, and it defies logic that the chemicals discussed in this assessment can cause many health conditions known to have very different modes of action.

ATSDR (2017a) discussed several limitations with studies it evaluated but appears to downplay their impact on the interpretation of study results. For example, the assessment 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 limited exposure information can result in major exposure misclassification, but that is not adequately considered in this assessment.

Similarly, ATSDR (2017a) discussed confounding, but tends to downplay it, 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 and is associated with decreased PD risk. Even if smoking or another factor isn't 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. Although literature search methods were described, it is not clear how studies were selected to be discussed in the text. That is, it appears that some studies were emphasized, while others were not, leading to a biased discussion of the evidence. Also, study quality was not evaluated in a systematic manner; sometimes it was not discussed at all. This is a major deficiency in the assessment because, as discussed in Section 3.3, study quality issues can impact the interpretation of results.

Perhaps most importantly, the criteria used in the ATSDR (2017a) assessment to determine whether chemicals in Camp Lejeune drinking water likely caused various diseases are not appropriate. ATSDR (2017a) claimed that it based its criteria on those put forth by IOM (2008) in its assessment, "Improving the Presumptive Disability Decision-Making Process for Veterans (2008)." These criteria were put forth as the basis for policy decisions, not for assessing causation. The requirements for categorizing levels of evidence for causation by IOM (2008) and ATSDR (2017a) are shown in Table 11.2. For each category, IOM (2008) requires more scientific evidence than ATSDR (2017a) does. For example, in the causal category, ATSDR (2017a) indicated consistent positive associations > 1.1 provide evidence for causation. There is no discussion of study quality for a causal conclusion – only study utility, though utility isn't defined, and there is no citation where the cutoff of 1.1 can be found. An association of 1.1 is generally considered quite weak.

Table 11.2 Categories for the Level of Evidence for Causation

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

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

Level of Evidence	IOM (2008)	ATSDR (2017a)
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.

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 the 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. Further, 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 reach similar conclusions for certain health outcomes (*e.g.*, benzene and leukemia/acute myeloid leukemia [AML]), as a whole, ATSDR (2017a) tends to conclude the evidence is stronger than other agency reviews, 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 childhood, adult, or general leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011a, 2020a), or did not draw any conclusions (ATSDR, 2019a; IARC, 2014a; IOM, 2015; NTP, 2015a). In contrast, ATSDR (2017a) concluded that the evidence for TCE and general 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."

In the ATSDR (2017a) discussion of PD, several studies of solvents are discussed. These studies are not informative with respect to any specific solvent. The assessment also discusses the Goldman *et al*. (2012) twin study, and acknowledges the small number of exposed cases, resulting in wide confidence intervals, but does not address any other aspects of study quality. ATSDR (2017a) does not thoroughly describe the two Camp Lejeune studies that were available at the time. Also, while the assessment notes that the studies evaluated mortality, it does not make a point of noting that these mortality studies are not informative for diseases with low mortality rates (as it mentions earlier in the document) such as PD, and it does not discuss other aspects of study quality or utility. It also describes risks as elevated, presumably based on risk estimates > 1, despite the 95% CIs being quite wide and the lower limit of the Cis being well below 1. Also, while ATSDR (2017a) calculated CIRs for other outcomes, none were calculated for PD. Despite the CIR not being a valid metric itself, if CIRs for the reported PD risk estimates in the Bove *et al*. (2014a) study were calculated, they would be 7.3 and 16.13, well above this assessment's cutoff of ≤ 2 or 3.

ATSDR (2017a) indicated that Lock *et al.* (2013) and IOM (2015) said there is "a plausible association between TCE exposure and [PD]" and that PD "may result from exposure to TCE and/or PCE." Neither of these conclusions indicate that it is at least as likely as not that these VOCs can cause PD. ATSDR (2017a) further stated:

> ATSDR concludes that the epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above. However, given the strong supporting mechanistic evidence for TCE, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and Parkinson disease**.
>
> For PCE, the epidemiological evidence is very limited and there is no available information on a plausible mechanism as there is for TCE. However, this may change if a metabolite of TCE that is common to PCE is found to be the agent causing damage to the dopaminergic neurons. Given what is presently known, ATSDR concludes that there is **below equipoise evidence for causation for PCE and Parkinson disease**.

Even using a biased framework, ATSDR (2017a) concluded evidence is below equipoise for PCE. However, evidence from mechanistic studies is not strong enough for a conclusion of equipoise and above for TCE. As noted by IOM (2008), "[I]f 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." ATSDR (2017a) has not demonstrated that mechanistic evidence is strong or that it demonstrates PD could be caused at human-relevant exposures, particularly those at Camp Lejeune.

It is notable that several of the Plaintiffs' experts rely on ATSDR (2017a), but don't acknowledge that this assessment does not discuss benzene or vinyl chloride with respect to PD risk and concludes evidence for causation is below equipoise for PCE, even when using a biased framework that was based on another framework intended to guide policy decisions. Plaintiffs' experts do not critically evaluate the methodology that ATSDR (2017a) used or demonstrate that it was sufficient to make an equipoise and above causal conclusion regarding TCE and PD.

11.2 Causes of PD

Plaintiffs' experts do not provide scientific support for their conclusion that most causes of PD are environmental.

Several of the Plaintiffs' experts discuss possible causes of PD and note that genetic factors only account for a small portion of cases (Boehme 2024; De Miranda 2024; Miller 2024; Costa 2024; Freeman 2024). They acknowledge that most PD cases are idiopathic, but then incorrectly assume that because known genetic causes can often be ruled out, chemical exposures are the mostly likely alternative cause. For example, Dr. Boehme (2024) states, "A number of factors are associated with the risk of PD, however, PD is largely thought of as a disorder brought about due to environmental contaminants."

Idiopathic means that a condition has no known cause, and idiopathic conditions can be, but are not always, spontaneous, which means that they arose without an identifiable trigger (*Dorland's Illustrated Medical Dictionary,* 2012). If the cause of a person's PD is idiopathic (which most of the Plaintiffs' experts acknowledge most PD cases are), it means that the cause is unknown. It does not mean an environmental exposure is the only possible alternative explanation.

11.3 Epidemiology Evidence

11.3.1 Methods

11.3.1.1 Study Identification and Selection

None of the Plaintiffs' experts systematically identified and selected epidemiology studies on TCE, PCE, or benzene exposure and PD.

The Plaintiffs' experts vary considerably in how they identified and selected studies for review and how they described their methods for doing so. For example, Dr. Boehme (2024) does not provide any information on how studies were identified, while Dr. Cannon (2024) provides a list of PubMed search terms. None of the Plaintiffs' experts describe a systematic and transparent process by which the scientific literature was searched. A systematic and transparent process for searching is needed to ensure there is no bias in the way that studies were identified and selected (*e.g.*, to ensure studies weren't selected because of their statistically significant findings) (Page *et al*., 2021).

Most of the Plaintiffs' experts do not evaluate all relevant epidemiology studies.

I identified nine studies that evaluated TCE, PCE, benzene, or vinyl chloride or working or being stationed at Camp Lejeune and risk of PD incidence or mortality. All of the Plaintiffs' experts cite Goldman *et al*. (2012) and at least some of the studies in populations at Camp Lejeune (Bove *et al*., 2014a; ATSDR, 2018b; Goldman *et al*., 2023). Some Plaintiffs' experts do not cite all available Camp Lejeune studies in their evaluation of the epidemiology evidence (*i.e*., Dr. De Miranda [2024] only cites Goldman *et al*. [2023] and Bove *et al*. [2014a]; Drs. Freeman [2024], Miller [2024], and Cannon [2024] do not cite ATSDR [2018b]). Several other studies of TCE, PCE, or benzene and PD were not reviewed by several, or in some cases any of the Plaintiffs' experts (*e.g*., Dorsey *et al*., 2024, Silver *et al*., 2014). It is not clear why these studies were excluded or omitted from their reviews of the evidence.

11.3.1.2 Study Quality

None of the Plaintiffs' experts evaluate the quality of the epidemiology literature and the impact of that quality on the interpretation of the results.

An evaluation of study quality is necessary to systematically and objectively identify study strengths and threats to validity (*e.g*., biases or confounding), and to determine how reliable the results of each study are for addressing the research question. The evaluation of quality aids in the understanding of the likelihood that study results may be due to bias, chance, or confounding and are important to consider when drawing conclusions about causation, or when determining whether the evidence is adequate to make such a determination (IARC, 2019). Quality should be evaluated for each independent study reviewed as well as for the literature as a whole (see Section 3). None of the Plaintiffs' experts thoroughly, transparently, or systematically assessed the quality of the epidemiology studies they included in their reports. Drs. Boehme (2024), Costa (2024), Freeman (2024), and Bird (2024) do not discuss study quality at all, while Drs. De Miranda (2024) and Cannon (2024) mention that there are some limitations to some studies, but they do not discuss these limitations in detail or discuss quality more broadly. Dr. Miller (2024) considers the literature to be "well-designed and very high-quality," but does not discuss quality in detail or justify this conclusion.

11.3.1.3 Statistical Significance

Several of the Plaintiffs' experts misinterpret statistical significance.

Several of the Plaintiffs experts conclude non-statistically significant risk estimates provide evidence of a causal association. As discussed below, while there are occasions when non-statistically significant results can occur when an association is causal, one should not conclude that non-statistically significant results provide evidence that this is the case, particularly if CIs are wide (Lash *et al*., 2021).

Similarly, Dr. Boehme states, "If the sample size is large enough, a meaningless measure of association (*e.g.,* odds ratio of 1.01 for a binary exposure of interest) will be statistically significant. Whereas the opposite stands such as in circumstances where a large measure of association is calculated but statistical significance is not reached due to small sample sizes, either overall or in specific groups being evaluated." This first sentence can be true; in some instances, a statistically significant small difference in a measure between two very large groups can be calculated that is not clinically meaningful (*e.g*., a 0.2 mmHg change in BP). The second sentence is not always true. There may be instances where an underpowered study fails to detect a true difference between two groups due to lack of precision, but it can also be the case that

as the sample size and the precision increase due to the reduced likelihood of sampling error, the CI narrows around a lower value within the range of the initial CI and is still non-significant. That is, one cannot assume that a non-significant effect would be significant if the sample size were larger. It is also possible that there is truly no effect.

When discussing Goldman *et al*. (2012), Dr. Miller (2024) states, "In addition, the study also found a significantly elevated risk for Parkinson's Disease in those twins who were exposed to PCE (Relative Risk Ratio=10.5, 95% confidence interval .97-113; this indicates a 10.5-fold increase, but the confidence interval ranges from 0.97-fold risk to 113-fold risk—when the confidence interval falls below 1 we consider this to not be statistically significant although this doesn't rule out biological relevance)." He goes on to say, "The exposure to PCE was highly associated with Parkinson's Disease, but the confidence interval indicated that the data were not robust enough to achieve statistical significance even though the data suggested up to a hundred-fold increase in risk (often a slightly larger study population would allow such an association to achieve statistical significance)." He further states, "The 95% confidence interval suggests that if one repeated the study 100 times that the same results would be found 95% of the time."

A CI captures the statistical significance of an effect estimate and provides a measure of the precision of an effect estimate; a narrower CI indicates more precision, and a wider CI reflects less precision. 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). It is always possible that the true effect will fall outside of the range of the CI (Lash *et al*., 2021; Ahlbom, 1993).

The CI is not meaningful, however, 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 sample may not reflect the true risk in the underlying population and, while increasing the sample size of a study may result in increased precision, it may not reflect an increase in precision around the true effect estimate. That is, if the sample is biased, risk estimates could be different and may even occur outside of the original CI (Lash *et al*., 2021).

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.

With respect to large samples sizes, in some cases, the Plaintiffs' experts seem to interpret risk estimates as fact because of the large effect measure estimated. For example, Goldman *et al*. (2012) reported an RR = 8.9 (99% CI: 1.7-47), which several Plaintiffs' experts stated was strong evidence for a joint association between TCE and PCE exposure and PD. While a true association is possible, it is more likely that this is effect size magnification, which occurs when risks estimated from small sample sizes are overestimated (Button *et al*., 2013; Miller *et al*., 2020). As David Miller *et al*. (2020) said, "Stated mathematically: conditional on a result passing some predetermined threshold of statistical significance, test level, or magnitude, the estimated effect size is a biased estimate of the true effect size with the magnitude of this bias inversely related to power of the study." In other words, when a study reports a large and statistically

significant risk estimate based on a small number of study participants, this result is likely to be a result of a biased sample and not necessarily indicative of the true magnitude of risk.

Finally, several Plaintiffs' experts indicate the CIR provides meaningful information regarding evidence for a causal association. As noted in Section 11.1, this seems to be a work-around when statistical significance is not achieved. It is not generally accepted as a measure of risk in the epidemiology community. I am not aware of any epidemiology textbooks or peer-reviewed environmental epidemiology studies that use this metric. Regardless, the CIR for this estimate from Goldman *et al*. (2012), for example, would be 47 ÷ 1.7 = 27.6, which is much higher than the threshold of 2 or 3 noted by ATSDR (2017a) for "adequate" precision.

11.3.1.4 Population Attributable Fraction

Dr. Boehme inappropriately calculated attributable risk of PD due to TCE/PCE at Camp Lejeune.

Dr. Boehme (2024) states:

> It is highly improbable the difference in the risk of PD between Camp Pendelton and Camp Lejeune [in Goldman *et al.*, 2023], in closely matched cohorts of both military personnel and civilians is due to genetic factors. This is illustrated by calculating the excess attributable risk percent using data from this study. The attributable risk percent for developing PD due to TCE/PCE exposure in this population [Camp Lejeune] is 44.7%, meaning 44.7% of the PD risk is explained by exposure to TCE/PCE at Camp Lejeune, the only major difference between the two populations.

In her conclusions, she states "the attributable risk proportion" is 42% (Boehme, 2024). Dr. Boehme provides no information on how she calculated this percent/proportion or why the numbers in the body of her report and conclusion are not the same.

What Dr. Boehme calls an attributable risk percent/proportion is commonly referred to as a PAF. A PAF is defined as the proportion of cases of an adverse health condition in the population (in this case PD) that can be attributed to an exposure and that could have been eliminated had exposure been removed from the population (Khosravi *et al.*, 2021). There are three major assumptions that must be met for this calculation to be valid: 1) the exposure can cause the condition; 2) if the exposure is removed, the risk of the condition in those who were exposed immediately becomes the same as those who were never exposed; and 3) removing the exposure does not affect other risk factors for that condition (Counil, 2021; Khosravi *et al.*, 2021; Levine, 2007; Rockhill *et al.*, 1998).

Dr. Boehme does not demonstrate that any of these assumptions are met. Goldman *et al.* (2023) did not calculate any chemical-specific risk estimates, so no calculated risk can be attributed to any specific chemical. In addition, as discussed throughout my report, the evidence does not support TCE or PCE as a cause of PD (*i.e.*, assumption 1 is not met). If neither VOC can cause PD, then they cannot be responsible for any proportion of the cases. It is also notable that assumptions 2 and 3 have not been demonstrated in any study cited by Dr. Boehme.

11.3.2 Epidemiology Studies

11.3.2.1 Goldman *et al*. (2012)

All of the Plaintiffs' experts suggest the twin study conducted by Goldman et al. (2012) provides strong evidence of an association between TCE and PD.

All seven of the Plaintiffs' experts cite the Goldman *et al*. (2012) case-control study in twins as evidence for an association between TCE and PD, and most also cite it as evidence for an association of PCE and PD. Drs. Boehme (2024), Miller (2024), Cannon (2024), and Bird (2024) all claim that Goldman *et al*. (2012) is a strong study that is key to establishing a relationship between TCE or PCE and PD. Dr. Bird (2024) states it is "a study of extremely high-quality design," and Dr. Miller (2024) states that the authors "used rigorous methods to ensure diagnostic accuracy and to assess exposures." Dr. Cannon (2024) states, "The key study is the Goldman *et al*. 2012 twin study [that] found high elevations in risk for both PCE and TCE with evidence of an exposure-response relationship for exposure duration and cumulative exposure."

As noted in Section 11.3.1, none of the Plaintiffs' experts evaluated study quality systematically or the study results within the context of the study strengths and limitations. The most critical limitation in this study is that some exposure misclassification was likely caused by the indirect nature of the exposure assessment, which was based on self- or proxy-reported lifetime job and hobby histories. The authors acknowledged the imprecision in their exposure estimates but assumed that this exposure misclassification would bias results towards the null. However, this assumption is incorrect because, when evaluating categories based on continuous data, as Goldman *et al*. (2012) did, non-differential misclassification can result in bias either toward or away from the null (Dosemeci *et al.*, 1990; van Smeden *et al*., 2020).

In addition, relying on proxy-responders for lifetime job and hobby histories could have resulted in further exposure misclassification, and the proxy response rate was much greater for cases (46.5%) than controls (18.2%). Results for any TCE exposure and TCE and PCE exposure combined after removing pairs with a proxy respondent were no longer statistically significant (TCE OR = 6.0, 95% CI: 0.7-50; TCE and PCE OR = 7.0, 95% CI: 0.9-57). Exposure information was also collected after PD diagnoses, which could have resulted in recall bias.

Regarding the study population, there was a high non-response rate (60-63%) in both cases and controls and it is unknown how those who participated may have differed from those who did not. Risk estimates were consistently elevated in analyses for TCE, PCE, and TCE and PCE combined, but few cases were exposed to any TCE (n = 10) or PCE (n = 5). The small sample size and small number of cases resulted in a lack of precision, wide CIs, and possibly effect size modification (Miller *et al*., 2020).

Finally, the discordant twin pair design may have eliminated some concern over confounding by unrecognized genetic and shared environmental factors during participants' upbringing, but it does not account for other behavioral and environmental factors, particularly those occurring in adulthood, like alcohol use and other chemical/occupational exposures, so some residual and uncontrolled confounding is likely.

These quality issues are major threats to the validity of the study. Given these major limitations, and the small sample sizes and large confidence intervals, this study does not provide sufficient evidence of a causal association between TCE or PCE and PD.

11.3.2.2 Camp Lejeune Studies

All of the Plaintiffs' experts cite three epidemiology studies conducted in overlapping populations of Marines and Navy personnel or civilians stationed or working at Camp Lejeune in their evaluation of the epidemiology evidence (Bove *et al*., 2014a; ATSDR, 2018b; Goldman *et al*., 2023); most also cite Bove *et al*. (2024a) or the pre-print of this paper (Bove, 2024b). The Plaintiffs' experts cite these studies as evidence that TCE causes PD and most also cite these studies as evidence that PCE causes PD. Dr. Bird (2024) cites these studies as evidence that benzene and vinyl chloride cause PD, and Dr. Boehme (2024) cites these studies as evidence that VOCs more generally cause PD. I review these studies in detail in Section 5; this includes an evaluation of study quality and an interpretation of results in the context of study quality. In addition, I review the studies that evaluated TCE or PCE specifically (Bove *et al*., 2014a; ATSDR, 2018b) as part of my review of epidemiology evidence for each chemical and integrated the epidemiology evidence with the toxicology and mechanistic evidence in Sections 6 and 7, respectively.

None of the Plaintiffs' experts systematically and completely evaluate the quality of studies conducted at Camp Lejeune or the impact of study quality on the interpretation of results.

Three studies in Camp Lejeune evaluated PD risks among Marines or Navy personnel stationed at Camp Lejeune and two studies evaluated PD risks among civilian workers on base. While all of these studies used populations that overlapped to various degrees, there was variation among studies with respect to the methods used to recruit or assemble the study populations, characterize exposures, and address confounding. As described in detail in Section 5, these studies all had several methodological limitations, most notably a high likelihood of exposure misclassification, a lack of adjustment for relevant covariates like alcohol use, and a serious potential for selection bias.

The Plaintiffs' experts did not systematically evaluate the results of these studies in the context of their study quality. Plaintiffs' experts either did not mention study quality at all or noted particular limitations and strengths in a seemingly *ad hoc* manner. For example, in her review of ATSDR (2018b), Dr. Boehme (2024) states, "This study deployed surveys to people who had lived and worked at Camp Lejeune and as a comparison Camp Pendleton with a 31% response rate," but she did not indicate whether those who responded were different from those who did not or how the response rate may have impacted the interpretation of the results. She also does not systematically discuss response rates of other studies she reviewed.

All of these studies were likely subject to exposure misclassification, both in analyses in which everyone at Camp Lejeune was considered exposed without regard to specific chemicals (*e.g*., in analyses of all CL Marines and Navy Personnel at Camp Lejeune compared to all Marines and Navy personnel at Camp Pendleton), and in analyses of risks associated with estimated chemical exposures. There were time periods where the levels of the chemicals of interest in the water at Camp Lejeune were below the level of detection; Marines and Navy personnel stationed at Camp Lejeune during this time period would not have been exposed. For example, there were only trace levels of contaminants of concern in water samples tested on October 30, 1980 (Hennet, 2024).

Even when evaluating exposure to specific chemicals based on modeled drinking water concentrations, there was likely 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). It is guaranteed to bias associations towards the null only under specific conditions (van Smeden *et al*., 2020). It has been demonstrated that when evaluating categories formed from continuous exposure measurements (Flegal *et al*., 1991) or multiple exposure categories (Dosemeci *et al*., 1990; van Smeden *et al*., 2020), similar to what was modeled and estimated in ATSDR (2018b), non-differential misclassification can result in bias either toward or away from the null. Bove (2024a) agreed that nondifferential exposure measurement error could lead to bias towards or away from the null stating, "It could go any which way, and that's why it makes it even more difficult, when you have exposure misclassification, to interpret an exposure-response relationship."

All of the studies likely had some selection bias. Because there were no records of who was on base when, many of the studies relied on partial records and mail surveys (ATSDR 2018b), or recruitment through health systems (*e.g*., VA and Medicare in Goldman *et al*. [2023]).

In ATSDR (2018b), the authors actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

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

While none of the Plaintiffs' experts address possible selection bias in ATSDR (2018b), Dr. Miller (2024) notes the importance of controlling for this in the Goldman *et al*. (2023, 2024) studies, saying that these studies appropriately "stopped [collecting] incident case data after the VA announced that it would cover Parkinson's disease (January, 2017). This exclusion was appropriate in that it prevented overestimation errors due to veterans seeking care after hearing that the condition would be covered."

Many of the Plaintiffs' experts do not acknowledge that all Camp Lejeune studies have some degree of overlap and are primarily conducted by the same researchers.

Bradford Hill (Hill, 1965) noted that evidence for a causal association is stronger if it has "been repeatedly observed by different persons, in different places, circumstances and times." Most Camp Lejeune epidemiology studies that evaluated PD were conducted by a single researcher (Dr. Bove), in one location (Camp Lejeune), during a discrete time period. The populations in these studies are overlapping to various degrees, and therefore they cannot be treated as independent evaluations in independent populations.

None of the Plaintiffs' experts appropriately addressed the lack of exposure specificity in the studies at Camp Lejeune in their evaluations of the relationship between each chemical and PD.

Most of the studies were not able to evaluate the association between specific chemical exposures at Camp Lejeune and PD risk. Because there were multiple contaminants in the water supply at Camp Lejeune simultaneously at certain points in time, it was difficult for the authors of the studies in Camp Lejeune to tease apart the specific chemical-PD relationships. Several studies chose not to evaluate specific chemicals at all and simply evaluate risk of PD associated with being assigned or employed at Camp Lejeune compared to PD risks in the US general population or in those assigned or employed at Camp Pendleton (*e.g.*, Goldman *et al*., 2023), while others attempted to estimate individual-level exposures based on modeled levels of contaminant in the water supply when people were on base (*e.g.*, ATSDR, 2018b). But even when attempts were made to evaluate individual chemicals, the chemicals concentrations were often so correlated that an independent evaluation of risk to exposure to a specific chemical was not possible (*e.g.*, in ATSDR [2018b], in the water system supplying the Marines and Navy personnel, there was complete correlation [gamma coefficient > 0.99] between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs, and there was a correlation of ~1 between TCE and PCE in the analysis for the civilian population). In all of the studies at Camp Lejeune it is possible that some participants were likely exposed to several VOCs in the water during their time on base.

Plaintiffs' experts do not address the inconsistencies of results reported in the Camp Lejeune studies.

The Plaintiffs' experts do not provide any discussion on where results of the same population disagree. 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 PD. Most risk estimates were statistically null, and the few statistically significant risk estimates were not reported across other analyses of the Camp Lejeune population. For example, the risk of PD in civilians varied from that estimated for Marines and Navy personnel in ASTDR (2018b). When compared to those at Camp Pendleton, ATSDR (2018b) reported that Marines and Navy personnel at Camp Lejeune did not have any changes in risk of PD incidence with increasing cumulative exposure to TCE (OR range: 0.29-0.87). Similarly, there were no changes in risk of PD incidence when comparing those with medium (110 to < 11,030 µg/L-mos) or high (≥ 11,030 µg/L-mos) TCE exposures to those with low (< 110 µg/L-mos) exposure in the Camp Lejeune cohort (OR range: 0.33-1.00). There were also no patterns of increasing risk with increasing exposure level in either analysis (*i.e.*, the highest risk estimates were in the medium exposure category and the lowest risk estimates in the highest exposure category). When compared to civilian employees at Camp Pendleton, employees at Camp Lejeune had an increased risk for PD incidence with medium levels of cumulative exposure (OR = 3.47, 95% CI: 1.18-10.22), but not with low (OR = 2.78, 95% CI: 0.87-8.94) or high (OR = 2.86, 95% CI: 0.67-12.13) levels. In analyses comparing those with medium and high cumulative exposures in Camp Lejeune to those with low exposures, no associations were reported (OR range: 1.81-2.03) though a positive monotonic exposure-response relationship was observed.

This discrepancy in risk between two populations, both exposed at Camp Lejeune, in the same study is not addressed by most Plaintiffs' experts and is crudely addressed by others. For example, Dr. Costa states that the differences in risk were "due to the fact that PD is a disease of old age, and at the time of the survey only 7% of the marines were >65 years old, *versus* 49% of the civilians." Dr. Boehme notes that the "younger military population included in this survey contributed to very low occurrences of PD within that population resulting in sparse data." It is reasonable to expect more cases to occur in an older population since PD is associated with age, but if TCE or PCE exposure were to cause PD, one would expect that risk estimates from exposure to TCE or PCE would not all be < 1 in a population that was followed for 28-38 years after exposure, as was reported for the Marines and Navy personnel. The average duration of time between the beginning of residence at Camp Lejeune and PD diagnosis was 33.9 years, and > 85% of the cases occurred within 40 years of the first assignment at Camp Lejeune in Goldman *et al*. (2023). If the

exposures at Camp Lejeune did accelerate the progression of PD as reported in Goldman *et al*. (2024), it is likely that there was a sufficient duration of time to capture cases even in a slightly younger population in ATSDR (2018b).

Plaintiffs' experts do not consider how limitations of Goldman et al. (2024) impact the interpretation of results.

Several experts cite Goldman *et al*. (2024) as evidence of people at Camp Lejeune having more aggressive or accelerated progression of disease (Costa, 2024; Boehme, 2024; Miller, 2024; Freeman, 2024; Bird, 2024). Goldman *et al*. (2024) evaluated the time to psychosis, fall, fracture, or death among individuals with PD who had been stationed at Camp Lejeune between April 1975 and December 1985 and had at least some VOC exposure at their residence compared to those with no VOC exposure at their residence. This time period (1975-1985) is when the highest potential exposures to VOCs occurred on base.

The number of control subjects that experienced psychosis, falls, or fractures were quite low in the control group, making estimated risks unstable.

Further, Goldman *et al*. (2024) stated they "had exposure estimates only for residential water supplies. Veterans would also have been exposed to VOCs through water sources where they worked, trained, and exercised, in addition to potential exposure through vapor intrusion into dwellings. Our inability to account for these nonresidential exposures would be expected to bias toward the null, obscuring rather than resulting in spurious associations." As noted above, bias towards the null would not occur in all situations, particularly if there is no association. Also, among exposed participants, individual level exposures were likely quite variable.

Setting aside the methodological issues with this study, it is notable that Dr. Boehme (2024) states, "Marines stationed at Camp Lejeune were diagnosed at a younger age when compared to civilian employees, and were noted to have a faster progression of disease." This is not true. In this study, the age at diagnosis was similar in the exposed and non-exposed groups ($p = 0.11$). While Goldman (2024) suggested that their inability to detect a difference in age of PD diagnosis was due to limited statistical power because of the young age of the cohort, this finding is consistent with the results of Goldman *et al*. (2023). Goldman *et al*. (2023) reported a slightly older mean age at PD diagnosis in veterans at Camp Lejeune (54.7 years) compared to veterans at Camp Pendleton (53.2 years) and a slightly longer duration of time between start of assignment on base and PD diagnosis in veterans at Camp Lejeune (33.9 years) compared to veterans at Camp Pendleton (32.2 years). If assignment at Camp Lejeune was associated with more accelerated disease, one would expect to see earlier onset of disease in veterans at Camp Lejeune compared to Camp Pendleton. None of the experts discuss this.

Finally, none of the experts discuss atypical PD, which is a type of parkinsonism that is distinct from PD that is characterized in part by more rapid progression of disease compared to PD.

11.3.2.3 Other Epidemiology Studies

Studies that reported null associations between TCE, PCE, or benzene and PD were overlooked by most of the Plaintiffs' experts.

Only two of the Plaintiffs' experts (Boehme, 2024; Freeman, 2024) cite two overlapping case-control studies in Finland (Nielsen *et al*., 2021; Sallmén *et al*., 2023). Dr. Costa (2024) cites Nielsen *et al*. (2021) in the materials considered section of his report but does not discuss or cite the study in his review of the evidence. Sallmén *et al*. (2023) describes the more recent evaluation in this population, which includes a

larger population followed over a longer duration of time compared to the prior analysis by Nielsen *et al*. (2021), and considers levels of cumulative exposure, which the prior study did not.

Dr. Boehme (2024, p.8) reviewed Nielsen *et al*. (2021) and stated that "occupations with a potential exposure to chlorinated hydrocarbon solvents, including TCE, had an increased risk of PD. The measures of association found in this study are likely a conservative estimate of the association between solvent and risk of PD as the use of occupation as a proxy to solvent exposure overestimates actual exposure thereby driving the association closer to the null." Dr. Boehme (2024) did not consider any additional strengths or weakness of the study, most notably that exposure was based on occupational job title reported on a single census, which likely resulted in exposure misclassification.

Dr. Freeman (2024) considered Sallmén *et al*. (2023) in his review and says, "More recently, a nationwide case-control study of PD and occupational exposure to organic solvents in Finland found that continuous cumulative exposure to chlorinated hydrocarbons (per 100 ppm years, 5-year lag) was associated with adjusted incidence rate ratio (IRR) of 1.235 (95% CI, 0.986,1.547), with stronger associations among women and among persons who had more census records.51 In their analysis of individual solvents including PCE, TCE, and benzene, higher levels of exposure were not associated with increased incidence of PD." He does not discuss study quality.

Only Dr. Costa (2024) reviewed Dorsey *et al*. (2024) a cohort study of lawyers working in an office tower that were potentially exposed to TCE or PCE from a dry-cleaner across the street from the tower. Dorsey *et al*. (2024) did not report any risk estimates but noted that there was no increased prevalence of PD in the tower attorneys compared to attorneys who worked ≥ 1 yr at other locations in the same city (*i.e*., Rochester, NY). Dr. Costa (2024) does not evaluate the quality of this study.

None of the Plaintiffs' experts reviewed a cohort study of microelectronics employees potentially exposed to TCE or PCE (Silver *et al*., 2014), or a case-control study of occupational exposure to benzene and PD mortality (Park *et al*., 2005). Neither study reported an association between any exposures and PD.

Like the studies included in Plaintiffs' experts' reviews, all of these additional studies had limitations, most notably a high potential for exposure misclassification. Regardless, they should have been included in the Plaintiffs' experts' evaluations of the epidemiology literature, as excluding them made the evidence seem more consistent than it actually is.

Several of the Plaintiffs' experts suggested that case studies provide additional evidence of a causal association between TCE and PD.

As described in Section 6.1.3, I only briefly discussed case studies in my evaluation of the epidemiology evidence because they do not provide evidence of a causal relationship. Case studies and case series are not suitable for causal inference because they lack key elements required to establish causation, such as a comparison group, control for confounding variables, and temporality. Without a comparison group, it is impossible to determine whether the observed conditions are caused by the exposure of interest or by other factors. In addition, these studies often do not establish temporality, a critical criterion for causality, as they may not confirm that the exposure preceded the outcome. Case series are also vulnerable to selection bias because they typically focus on unusual or rare events that may not represent the broader population. While useful for hypothesis generation, these limitations mean that causal relationships must be confirmed by studies with more robust study designs, such as cohort or case-control studies (Lash *et al*., 2021; Celentano and Szklo, 2019).

The case studies cited in the Plaintiffs' experts' reports provide historical context to show why solvents generally and TCE specifically were first identified as potentially associated with PD. However, due to

their limitations (*e.g.*, lack of an appropriate comparison group; an inability to control for potential confounders; potential selection bias), they do not provide evidence regarding whether a chemical can cause a specific health condition. As such, case studies do not and cannot provide evidence of a causal relationship between TCE and PD.

11.4 Experimental Evidence

Plaintiffs' experts' discussions of experimental studies do not support their conclusions that TCE is at least as likely as not a cause of PD in humans.

Dr. De Miranda (2024) cites or discusses the 12 available experimental animal studies evaluating TCE and PD, but no other expert evaluated all of these studies. In general, these experts overstate and misrepresent experimental evidence, particularly with respect to the magnitude of dopaminergic neuron loss, the consistency of study findings, and the relevance of study findings to PD in humans. Plaintiffs' experts acknowledge some, but not all, of the limitations of the experimental animal studies, including the high experimental doses and inability to fully replicate the progression and pathology of human PD in experimental animal models.

Some of the Plaintiffs' experts make factually incorrect statements regarding the toxicity and mechanistic evidence, demonstrating a lack of understanding of the underlying scientific literature. For example, Dr. De Miranda (2024) incorrectly cites Otsuki *et al*. (2016) as evidence of oxidative damage in dopaminergic neurons, but this study did not evaluate dopaminergic neurons. Overall, Plaintiffs' experts' discussions of the toxicity and mechanistic evidence do not support their conclusions that there is sufficient evidence of a causal association between TCE and PD in humans.

11.4.1 Study Identification and Selection

Most of the Plaintiffs' experts do not evaluate all relevant toxicity and mechanistic studies.

There are 12 available experimental animal studies that assessed TCE and PD: one subchronic inhalation study (Adamson *et al*., 2023), seven subchronic oral gavage studies (Gash *et al*., 2008; Liu *et al*., 2010, 2018; De Miranda *et al*., 2021; Ilieva *et al*., 2022, 2024; Srivastava *et al*., 2024), one subchronic i.p. injection study (Keane *et al*., 2019), one subacute oral gavage study (Sauerbeck *et al*., 2012), and two subacute i.p. injection studies (Guehl *et al*., 1999; Otsuki *et al*., 2016). Drs. Boehme, Bird, Cannon, Costa, Freeman, and Miller only cite or discuss two, nine, nine, nine, three, and eight of the 12 studies, respectively, indicating that their opinions are based on an incomplete evaluation of the relevant scientific literature.

11.4.2 Mode of Action

Plaintiffs' experts' conclusions regarding mechanisms by which TCE could cause PD are not supported by cited studies.

Dr. Boehme (2024) acknowledges that, in humans, "[t]he most common PD symptoms result from death or damage to neurons in the *substantia nigra*, an area near the base of the brain, resulting from the loss of 60-80% of dopamine-producing cells in this area." While Plaintiffs' experts note that some experimental animal studies caused statistically significant dopaminergic neuron loss in the SNpc associated with subchronic or subacute TCE exposures, none except Dr. Costa mention the magnitude of dopaminergic neuron loss. More importantly, none of the Plaintiffs' experts mention that, in all but one study (Keane *et*

al., 2019), the magnitude of loss was less than that required to produce clinical signs of PD in humans (discussed in Section 6.2).

Only Dr. De Miranda (2024) cites the studies by Otsuki *et al*. (2016) and Srivastava *et al*. (2024). However, Dr. De Miranda (2024) incorrectly cites Otsuki *et al*. (2016) as evidence that "oxidative damage is significantly elevated in dopaminergic neurons within the SN [*substantia nigra*] of animals exposed to TCE." Otsuki *et al*. (2016) did not evaluate markers of oxidative damage in dopaminergic neurons of the *substantia nigra* of TCE-treated animals. Moreover, Otsuki *et al*. (2016) reported that "no significant differences were observed among the experimental groups by biochemical and histopathological analyses" (*i.e*., TCE exposure caused no loss of dopaminergic neurons and no effects on levels of dopamine or dopamine metabolites), but Dr. De Miranda does not mention this. Similarly, Dr. De Miranda cites Srivastava *et al*. (2024) in support of her opinion that "inhalation and ingestion of TCE have been shown to cause dopaminergic neurotoxicity in experimental studies" (De Miranda, 2024). As noted in Section 6.2, Srivastava *et al*. (2024) stated that TCE exposure was associated with "[s]ignificant neuronal loss" in the midbrain, but the magnitude and statistical significance of TCE-induced neuron loss were not reported. Moreover, Srivastava *et al*. (2024) did not specifically evaluate dopaminergic neurons, but rather total neurons in the midbrain.

Several Plaintiffs' experts discuss Liu *et al*. (2010) as providing evidence of TCE-induced toxicity to SNpc dopaminergic neurons, but none mention that Liu *et al*. (2010) concluded that, while the results of their study demonstrated "some important features of Parkinsonism," the results "could be interpreted as a TCE-induced moderate injury in which there are no significant decreases of dopamine content in the striatum and no marked deficit of spontaneous locomotor activity in TCE-treated animals." These Plaintiffs' experts also did not mention that the magnitude of loss of dopaminergic neurons was less than that required to produce clinical signs of PD in humans (discussed in Section 6.2).

All Plaintiffs' experts except Dr. Bird cite or discuss the results of Liu *et al*. (2018) and Keane *et al*. (2019) as support for TCE-induced toxicity to SNpc dopaminergic neurons. However, Liu *et al*. (2018) concluded that "even prolonged administration of TCE was insufficient for producing a greater than 50% loss of nigral dopamine neurons, indicating that additional comorbid factors would be needed for mimicking the profound loss of dopamine neurons seen in PD". None of the Plaintiffs' experts mention that the magnitude of loss of dopaminergic neurons and dopamine levels in SNpc were less than that required to produce clinical signs of PD in humans (60-80 and 70-80%, respectively) (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). Similarly, Keane *et al*. (2019) said, "TCE or TaClo did not appear to lead to acceleration of motor or cognitive deficits in either wild type or A30P mutant mice, potentially because of the modest reductions of [dopamine] neuronal number in the SNpc." The authors concluded, "It is possible that the levels of [dopamine] cell death in the SNpc of treated animals are insufficient to cause motor dysfunction since over 70-80% SNpc cell death is required before behavioural deficits are seen" (Keane *et al*., 2019).

As discussed in Section 6.2, none of the available experimental animal studies, including Liu *et al*. (2010, 2018) and Keane *et al*. (2019), support TCE as a cause of PD in humans.

11.4.3 Relevance of High Doses

Only some of the Plaintiffs' experts acknowledge that single high doses in animal studies are not relevant to humans.

Regarding dose and dose-response, the available animal studies of TCE evaluated oral doses ≥ 200 mg/kg-day, i.p. doses ≥ 400 mg/kg-day, and inhalation concentrations of ≥ 50 ppm. As such, Dr. Boehme (2024), Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), and Dr. Costa (2024) acknowledge in their reports that markers of PD in animal studies evaluating TCE is primarily a high dose phenomenon, with Dr. Miller (2024) and Dr. Cannon (2024) further noting that the doses are much higher than those to which humans are exposed.

In addition, some of the tested doses were close to those causing unrelated toxic effects and even lethal effects in animals (ATSDR, 2019a). Many of the oral and intraperitoneal studies only used a single dose, which precludes a dose-response analysis (Gash *et al*., 2008; Liu *et al*., 2018; De Miranda *et al*., 2021; Ilevia *et al*., 2022, 2024; Srivastava *et al*., 2024; Keane *et al*., 2019; Saurbeck *et al*., 2012; Guehl *et al*., 1999; Otsuki *et al*., 2016).

Adamson *et al*. (2023) was the only study to use an inhalation exposure route, but they also used single high exposure concentrations of 50 ppm in rats and 100 ppm in mice, precluding a dose-response analysis. Dr. Boehme (2024), Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), and Dr. Costa (2024) highlight this study in their reports to make the argument that exposure to lower levels of TCE by an inhalation exposure route, which is most relevant to humans, can also induce dopaminergic neuron loss in experimental animals characteristic of PD.

However, Adamson *et al*. (2023) estimated the human equivalent dose in this study using an equation for estimating oral exposures, not inhalation exposures. Humans have a lower air intake per kg than rodents, so our intake is lower at any given air concentration (Rhomberg, 2009). Also, as noted by NRC (2009) in its report, "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects," "for equivalent inhalation exposures to TCE and other VOCs, internal doses are substantially higher in rodents than in humans (Bruckner *et al*., 2008). NRC (2009) further stated, "Mice and rats absorb more inhaled TCE and PCE, metabolically activate more of their absorbed dose, and inactivate epoxide metabolites less efficiently than do humans." Because rodents have substantially greater effects from exposures to chemicals *via* inhalation relative to humans, caution is warranted with respect to interpreting any potential relevance to humans (NRC, 2009).

While Dr. Miller (2024) acknowledges the high doses used in experimental animal studies in his report, he also makes two broad generalizations that are not scientifically supported. First, Dr. Miller (2024) states, "Given the increased rate of metabolism in rodents, it is common in acute and even chronic toxicology studies to use doses much higher than…seen in human exposures." Dr. Miller's citation for this statement, Walker *et al*. (2019), does not discuss this concept. While it is true that rodents have higher metabolic rates and shorter lifespans, physiological and metabolic differences between rodents and humans can lead to different toxicological responses, even at proportional doses. In addition, high doses in rodent studies can activate metabolic pathways or overwhelm detoxification mechanisms that would not occur at real-world human exposure levels (Aleksunes and Eaton, 2019; Faustman, 2019; Woutersen *et al*., 2020; Borgert *et al*., 2021). With respect to high doses in animal studies, Borgert *et al*. (2021) discussed the use of the MTD. The MTD is the highest dose that does not result in either death or a ≥ 10% reduction in body weight gain. This dose is generally orders of magnitude higher than human exposures and may result in kinetic changes with respect to how a chemical is metabolized and eliminated that do not occur at lower exposures (Borgert *et al.*, 2021). As stated by Borgert *et al*. (2021):

> The rationale for dosing at the MTD is to increase the statistical power of a study for detecting low-incidence effects, which would otherwise require a drastic increase in group sizes. However, the supposed power advantage of MTD-observed toxicity does not and cannot compensate for the inability of small group sizes in toxicity tests to predict whether adverse responses might occur at, often, very much lower doses produced by typical human exposure levels.

Second, Dr. Miller (2024) states in his report that, "For the majority of toxicants, it takes doses 10-100x more than what humans are exposed to in order to replicate similar symptoms or toxicity." However, the relationship between the dose or concentration of any toxicant that can cause a certain apical effect in experimental animals and the dose to which humans are exposed can vary depending on the specific toxicant, the route of exposure, species, and interindividual/intraindividual variability, among other factors (US EPA, 2011b). The available evidence suggests that the potential neurotoxic effects of TCE observed in animal studies are largely associated with high-dose exposures that far exceed those experienced in environmental settings.

11.4.4 Dose-Response

Only one study evaluated dose-response.

Dr. Boehme (2024), Dr. Miller (2024), Dr. Cannon (2024), and Dr. Costa (2024) claim that the effects of TCE on PD-related markers in experimental animals are dose-dependent. However, only one study (Liu *et al*., 2010) evaluated more than one dose. This study on its own does not provide sufficient evidence for dose-response, particularly when considering the authors stated that their results "could be interpreted as a TCE-induced moderate injury in which there are no significant decreases of dopamine content in the striatum and no marked deficit of spontaneous locomotor activity in TCE-treated animals."

The establishment of a dose-response relationship is an important consideration in evaluating the potential neurotoxicity of an agent. As described by US EPA (1998):

> Dose-response evaluation is a critical part of the qualitative characterization of a chemical's potential to produce neurotoxicity and involves the description of the dose-response relationship in the available data. Evidence for a dose-response relationship is an important criterion in establishing a neurotoxic effect, although this analysis may be limited when based on standard studies using three dose groups or fewer. The evaluation of dose-response relationships includes identifying effective dose levels as well as doses associated with no increase in adverse effects when compared with controls. The lack of a dose-response relationship in the data may suggest that the effect is not related to the putative neurotoxic effect or that the study was not appropriately controlled.

In support of dose-response, Dr. Cannon (2024) states, "While, by analogy and in view of the data provided by the research thus far discussed above, a dose response is expected, additional data are required. Broad measures of neurotoxicity in animal studies show dose response. PD specific endpoint studies are needed across a wide range similar to what has been conducted with TCE." It appears that the basis for his opinion regarding dose-response includes one study reporting decreases in brain growth, total protein, and DNA in rats exposed to 300-600 ppm PCE; one study reporting evidence of flash evoked potential in the visual cortex of rats exposed to 800 ppm PCE; and an additional set of studies showing loss of specific phospholipids, neurochemical alterations, and effects on glial cells in the brains of gerbils following chronic

treatment. None of these studies demonstrate dose-response, and the endpoints measured are not related to PD or the effects noted for TCE.

11.4.5 Inconsistent Study Results

The single TCE inhalation study reported inconsistent motor effects.

In a study that Dr. De Miranda co-authored, Adamson *et al*. (2023) subchronically administered a single 50 ppm or 100 ppm dose of TCE *via* inhalation (whole-body) to Lewis rats and C57BL/6 mice, respectively, and evaluated dopaminergic neuron pathology and motor behavior. Adamson *et al*. (2023) reported inconsistent effects on gait parameters in TCE-exposed rodents; some gait measures increased, some gait measures decreased, and some were unaffected. Had TCE caused these effects, one would have expected them to be consistent (*i.e*., all increased or all decreased). As such, this study does not provide evidence that TCE may cause PD in humans.

11.4.6 Systemic Toxicity

Alleged neurotoxic effects should be interpreted in the context of the presence or absence of systemic toxicity.

Plaintiffs' experts do not adequately consider the potential for systemic toxicity to confound behavioral effects attributed to TCE exposure in animals. According to US EPA (1998), "Understanding the interrelationship between systemic toxicity and behavioral changes (*e.g*., the relationship between liver damage and motor activity) is extremely important. Changes that are not dose dependent or that are confounded with body weight changes and/or other systemic toxicity may be more difficult to interpret as neurotoxic effects" (US EPA, 1998). For example, De Miranda *et al*. (2021) subchronically administered TCE or vehicle *via* oral gavage to rats once daily for 1, 3, or 6 weeks. The study authors reported effects on dopaminergic neurons and locomotor activity that they attributed to TCE exposure. However, De Miranda *et al*. (2021) reported reduced growth in TCE-exposed rats compared to controls (Supplemental Figure 1 in De Miranda *et al*. [2021]).[20] Because of the systemic toxicity in this study, changes in dopaminergic neurons and motor effects in TCE-exposed rats observed in this study cannot be reliably attributed to TCE exposure.

11.4.7 Pathology of PD in Humans

Animal models do not replicate the pathology and etiology of PD in humans.

Although PD-associated pathological outcomes were reported in rats and mice exposed to very high doses of TCE *via* oral gavage or i.p. injection, these animal models do not exactly mimic the etiology, progression, and pathology of human PD. Only Plaintiffs' expert Dr. De Miranda (2024) notes this limitation in her report.

Dr. De Miranda (2024) states, "Experimental models of TCE exposure can replicate hallmark cellular PD pathology with evidence for the same molecular mechanisms in the brain that are widely recognized as contributors to PD pathogenesis (*e.g*., mitochondrial and lysosomal dysfunction)," but acknowledges that,

[20] De Miranda *et al*., (2021) stated, "No significant body mass decrease was observed in any TCE Cohort," but they did not report whether this result was statistically significant. This conclusion is at odds with data that are presented in Supplemental Figure 1 of their study, which suggest that there were changes in body mass in the treatment group.

"as with any disease condition, experimental systems cannot replicate the complex conditions that occur in human populations." She further states that "while the dose used in some experimental model systems is considered high, the assumed resulting brain concentrations can still inform proof-of-principle mechanisms involved in parkinsonian neurodegeneration." However, there is no evidence that these MoAs can occur at lower concentrations or cause effects of sufficient magnitude to cause PD. As such, they do not provide proof of principal as Dr. De Miranda claims.

Perhaps more importantly, studies evaluating TCE and PD-associated pathological outcomes reported dopaminergic neuron loss that did not reach the 60-80% threshold noted by Dr. Boehme (2024) as being required to produce clinical symptoms of PD in humans (Bernheimer *et al*., 1973; Riederer and Wuketich, 1976; Hirsch *et al*., 1988; Fearnley and Lees, 1991; Zarow *et al*., 2003; NIH, 2024). The only study reporting dopaminergic neuron loss above this threshold was the subchronic intraperitoneal injection study by Keane *et al*. (2019). The dose and route of exposure in this study are not relevant to humans.

Finally, many animal models used behavioral testing as markers of PD symptoms (Adamson *et al*., 2023; Liu *et al*., 2010, 2018; De Miranda *et al*., 2021; Srivastava *et al*., 2024; Keane *et al*., 2019; Saurbeck *et al*., 2012; Guehl *et al*., 1999; Otsuki *et al*., 2016). Although the neuroanatomical components surrounding motor control may be similar in experimental animals and humans, manifestation occurs differently. In behavioral tests such as the rotarod and grid tests, which are "learned" tests, the behavioral tasks are reflective of bradykinesia (slowness of movement) and akinesia (loss of muscle movement), and not rigidity or tremor, both of which occur in human PD (Potashkin *et al*., 2010). In addition, some tests, such as the rotarod test, are not good measures of behavior changes associated with dopaminergic neuron degeneration (Lock *et al*., 2013). Many animals are also excluded from the final analysis if the behavioral task is not learned.

Overall, while Plaintiffs' experts discuss molecular mechanisms hypothesized to be important in proposed TCE MoAs for PD, even they acknowledge that there is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD.

11.5 Bradford Hill Assessments

All of the Plaintiffs' experts evaluated causation using at least some of the considerations proposed by Bradford Hill (Hill, 1965) (Section 3.4). As discussed below, in several instances, the Plaintiffs' experts did not appropriately apply these considerations in their evaluations. As a result, their causal conclusions are not supported.

11.5.1 Strength of Association

Several Plaintiffs' experts state that weak associations are strong.

All of the Plaintiffs' experts that addressed strength of association concluded that this consideration was met. However, there is no scientific consensus or standard convention that defines what constitutes a strong association, and the Plaintiffs' experts do not provide any objective criteria for evaluating this. For example, Dr. Boehme (2024) provides no threshold for a strong association, merely stating, "The strength of association between TCE/PCE and PD or PD mortality was consistently very strong. Regardless of the population being assessed or how the exposure and/or outcome were being measured, the strength of association was consistently strong." Other Plaintiffs' experts appear to define a strong association as being > 1.1 based on ATSDR (2017a). For example, Dr. Bird (2024) states, "Studies of Camp Lejeune personnel demonstrate risks of greater than 1.1 for exposure to the Camp Lejeune chemical TCE and Parkinson's

Disease." There is no citation for the threshold of 1.1, although I assume that it was based on the ATSDR (2017a) report. As discussed above in Section 11.1, ATSDR (2017a) indicated consistent positive associations > 1.1 provide evidence for causation, but this document provides no citations or rationale for this threshold.

An association of 1.1 is generally considered quite weak. Wynder (1990) noted that "when the odds ratios are 2 to 1 or less, the possibility that the finding is artificial and a consequence of problems in case-control selection or due to the presence of confounders and biases needs to be carefully considered." Further, in a recent review of the epidemiology literature on pyrethroids, 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 use of "*e.g.*" instead of *i.e.* by US EPA (2019) demonstrates that these aren't hard cutoffs for categorizing strength of evidence. Still, this provides some guidance that risk estimates < 2 are not even moderately strong.

The reason why strength is a consideration at all is because weaker estimates are more likely to be subject to bias. Even a small amount of bias or confounding could influence a risk estimate by 10% (Wynder, 1990). As discussed in 10.3.1.2, the Plaintiffs' experts do not provide a systematic evaluation of study quality or provide evidence that risk estimates of 1.1 or higher are not potentially being influenced by bias or confounding.

Dr. Bird (2024) does not interpret strength appropriately.

Dr. Bird (2024) states, "Strength of association is demonstrated by statistical significance." He later states, "It should be noted that statistical significance is not itself determinative of causation; rather, it helps to explain the likelihood one would see a disease in a given population *versus* a control group. Therefore, studies with confidence intervals that include 1.0 do not establish that an agent does not cause a given disease, but rather that the subject disease may not be more prevalent in the exposed group than in a control group."

Strength of an association has to do with the magnitude of the association, not with its statistical significance (Hill, 1965). Statistical significance plays no role in the interpretation of the strength of the association, only whether one can reasonably exclude chance as an explanation (see Sections 3.1.1 and 10.3.1.3). Bradford Hill (1965) stated, "Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."

Strong associations may not reflect risks in the underlying population due to bias or chance.

As discussed in Section 11.3.1.3, very large risk estimates (*e.g.*, ≥ 5) may be due to artificially inflated effect sizes (*e.g.*, effect size magnification) or be reflective of a small sample size (Button *et al.*, 2013; Miller *et al.*, 2020). When considering the strength of association, none of the Plaintiffs' experts considered whether risk estimates reflected the underlying population or were more likely due to bias or chance.

11.5.2 Consistency

Plaintiffs' experts state that this criterion is met without fully considering whether associations have been "repeatedly observed by different persons, in different places, circumstances and times" (Hill, 1965).

Bradford Hill (Hill, 1965) stated that associations should be "repeatedly observed by different persons, in different places, circumstances and times." The evidence considered by most of the Plaintiffs' experts is from four studies conducted in populations at Camp Lejeune (Bove *et al*., 2014a, 2024a,b; ATSDR 2018b; Goldman *et al*., 2023) and one case-control study in twins (Goldman *et al*., 2012). There are only two lead authors of these five papers (*i.e*., Drs. Goldman and Bove) and the studies in Camp Lejeune are not conducted in independent populations (there is some degree of overlap between the Marines and Navy personnel and civilian populations between those studies).

The Plaintiffs' experts do not address how these factors impact the assessment of consistency. For example, Dr. Miller (2024) notes that the Camp Lejeune population was composed of "numerous cohorts" because personnel may have served over the course decades and been exposed at different times of the year and over different periods. However, there were certainly overlapping populations in the Camp Lejeune studies, and these studies were not conducted by independent investigators.

Drs. Boehme, Cannon, and Costa all conclude that results were consistently in the same direction and statistically significant. The only way they could come to this conclusion is to ignore all the null results (including those < 1) reported in the available studies and ignore the different results for Marines and Navy personnel and civilian employees and Camp Lejeune.

The Plaintiffs' experts do not consider consistency across the available epidemiology literature.

As discussed in 10.2.3.3, most of the Plaintiffs' experts did not review the entirety of the literature on TCE, PCE, or benzene and PD, and most of the studies omitted from their review consistently reported risk estimates that were null and close to 1. The results from these studies are inconsistent with the results reported in Goldman *et al*. (2012), which many of the Plaintiffs' experts rely on heavily in their evaluation of the epidemiology evidence.

Some Plaintiffs' experts do not interpret consistency appropriately.

Dr. Bird says the Gash *et al*. (2008) neurological evaluation of 30 workers with chronic TCE exposure and an animal study on mitochondrial neurotoxicity from TCE exposure provide evidence of consistency. Whether or not these two studies are consistent with each other does not address whether studies of TCE and PD are consistent. Dr. Freeman bases his conclusion on a single meta-analysis of solvents by Pezzoli and Cereda (2013). This study did not evaluate TCE specifically and did not include all relevant studies of TCE and PD.

11.5.3 Specificity

All of the Plaintiffs' experts agree that specificity as defined by Bradford Hill (Hill, 1965) is not met.

11.5.4 Temporality

All of the Plaintiffs' experts concur that exposure occurred prior to PD diagnosis in epidemiology studies.

11.5.5 Dose-Response

The Plaintiffs' experts disagreed on whether the dose-response was met.

Drs. Costa, Freeman and Miller all report that the evidence supports dose-response. Dr. Costa does not cite any study specifically; he states more generally that "The presence of a biological gradient is indicated by increasing PD incidence associated with higher and longer exposures to TCE." Dr. Freeman cites the case-control study by Goldman *et al*. (2012) as evidence of dose-response, reporting that the odds of PD significantly increased with level of exposure. Dr. Miller states, "Human and animal studies provide excellent support for biological gradient and dose-response," but does not cite any specific epidemiology studies as evidence of a dose-response relationship.

Dr. Boehme, citing both human and animal studies, reports that the criterion is only "partially met" because some studies consistently found that higher exposure to TCE/PCE led to a higher risk of PD, more severe PD symptoms, and faster disease progression, but other studies demonstrate a non-monotonic dose-response. Dr. Bird is not clear on whether he concludes the consideration is met, focusing on the challenge of different absorption mechanisms in children compared to adults. With respect to PCE, Dr. Cannon states the dose-response consideration is "not directly met" because, while animal neurotoxicity studies have shown a dose-response, there have not been PD-specific endpoint studies across a wide range of PCE doses, which would be required to conclusively demonstrate dose-response.

As discussed in Section 6.5 and 7.5, only two epidemiology studies assessed dose-response specifically for exposures to TCE and PCE (Sallmén *et al*., 2023; ATSDR, 2018b). [21] Neither study provides consistent evidence for an increased risk of PD with increased exposure.

Bradford Hill (1965) was not referring to dose-response in animal studies.

By biological gradient, Bradford Hill (1965) meant that if increasing exposure was associated with increasing risk, this would add to the evidence of a causal association. Bradford Hill (1965) intended this criterion to be specific to human studies, not animals, acknowledging that, "often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it" (Bradford Hill, 1965).

Several of the Plaintiffs' experts cited animal data in their evaluation of the evidence supporting a dose-response. For example, Dr. Bird cited a dose-dependent loss of dopaminergic neurons in a study by Liu *et al*. (2010). Dr. Bohme also relies, at least in part, on animal studies as she states, "laboratory and case reports/studies illustrate how as the does [*sic*] of exposure increases the risk and severity of symptoms increase. Here [*sic*] are also studies that demonstrate a non-monotonic dose response." Dr. Miller (2024), Dr. Cannon (2024), and Dr. Costa (2024) also claim that the effects of TCE on PD-related markers in

[21] Bove *et al*. (2024a) evaluated risk of PD by duration of assignment at Camp Lejeune. This study does not evaluate chemical specific risks, and evaluation of duration of assignment does not reflect a potential dose-response association for any of the chemicals of interest because levels of chemicals varied over time. Someone who had a longer duration of assignment at a time period with a lower concentration of VOCs in the water could have had a lower exposure (*i.e*., dose) than someone who had a shorter duration of assignment when concentrations were high. In addition, individual-level exposure doses were highly dependent on not only concentrations in the water sources used, but also water consumption and specific behaviors (*e.g*., frequency and duration of showering).

experimental animals are dose-dependent. I discuss biological gradient in animal studies in more detail in Section 11.4.4. Briefly, only one study (Liu *et al*., 2010) evaluated more than one dose and outcomes consistent with PD. Other studies that evaluated neurotoxicity evaluated endpoints that have not been associated with PD.

Dr. Bird's discussion of children and dose-response at Camp Lejeune is incorrect.

Dr. Bird states, "[F]urther complicating the dose-response relationship is that amongst the exposed people at Camp Lejeune there were children as well as adults." While it is true that there were children of Marines and Navy personnel living on base, there were no exposures to children evaluated in the studies at Camp Lejeune that evaluated PD. The dose-response evaluation is specific to the exposure-outcome relationship being evaluated, so childhood exposures at Camp Lejeune do not complicate the evaluation of a dose-response for TCE, PCE, benzene, or vinyl chloride and PD in adults at Camp Lejeune.

11.5.6 Biological Plausibility

11.5.6.1 TCE

Mechanistic evidence from TCE toxicity studies does not support a causal association.

Plaintiffs' experts generally conclude that there is sufficient evidence from toxicity studies to support biological mechanisms by which TCE may cause PD in humans, including the loss of dopaminergic neurons, the formation of the metabolite TaClo, activation of LRRK2, mitochondrial dysfunction, oxidative stress, microglia activation, neuroinflammation, accumulation of α-synuclein.

However, as noted above, there is no laboratory animal model that exactly mimics the etiology, progression, and pathology of human PD. For example, Dr. De Miranda (2024) states, "Experimental models of TCE exposure can replicate hallmark cellular PD pathology with evidence for the same molecular mechanisms in the brain that are widely recognized as contributors to PD pathogenesis (*e.g*., mitochondrial and lysosomal dysfunction)," but acknowledges that, "as with any disease condition, experimental systems cannot replicate the complex conditions that occur in human populations."

Of particular concern is the doses used in all animal models. PD has a threshold MoA, meaning that it will not develop unless the magnitude of biological changes reaches a tipping point. All studies of TCE and PD have assessed only extremely high concentrations and thus provide no evidence that these mechanisms could occur at lower concentrations.

For example, with respect to evidence of dopaminergic neuron loss, none of the Plaintiffs' experts acknowledge that, in all but one study (Keane *et al*., 2019), the magnitude of dopaminergic neuron loss was less than that required to produce clinical signs of PD in humans (discussed in Section 6.2). In addition, several Plaintiffs' experts discuss the production of the TCE metabolite TaClo and its potential role in PD. However, Dr. Cannon (2024) acknowledges "there is some controversy on whether TaClo is formed in mammals exposed to chloroethylenes." As discussed in Section 6.3, findings from studies of TaClo are inconsistent and do not suggest specificity for the dopaminergic system or selectively toxic to dopaminergic neurons (Storch *et al*., 2006; Lock *et al*., 2013).

Similarly, LRRK2 activation only occurred with exposure to TCE at doses ≥ 200 mg/kg-day. De Miranda *et al*. (2021) concluded that the mechanism by which TCE may activate LRRK2 "is less clear" and that the

extent that LRRK2 activation by chemicals may affect the dopaminergic system of humans carrying LRRK2 mutations "is unclear."

11.5.6.2 PCE

No toxicity studies have evaluated the relationship between PCE exposure and PD.

No PCE toxicity studies have evaluated PD. Plaintiff's experts' conclusions have been drawn regarding PCE based on the hypothesis that a common metabolite of PCE and TCE can cause PD. For example, Dr. Cannon (2024) said, "PCE and TCE have similar metabolites, extending the weight of evidence beyond simple analogy to biological plausibility when considering the role of chloroethylenes in PD relevant neurotoxicity." However, as discussed in Section 6.4, experimental evidence does not support a causal relationship between TCE exposure and PD in humans, even *via* a metabolite. Thus, there is no evidence that PCE is a biologically plausible cause of PD.

Dr. Cannon provides the greatest focus on PCE and PD and concludes that, "Tetrachloroethylene (PCE) is at least as likely as not a cause of Parkinson's disease (PD)" (Cannon, 2024). However, Dr. Cannon's conclusions regarding mechanisms by which PCE could cause PD are not supported by the cited studies, specifically regarding mitochondrial toxicity. Dr. Cannon (2024) states that, "mitochondrial toxicity is a critical mechanism of PD," and cites the studies by Zhou *et al*. (2017), Ogata and Hasegawa (1981), Miyazaki and Takano (1983), and Fiorucci *et al*. (1988), stating:

> One study found that PCE had an even greater effect (equimolar comparison) on mitochondrial pathways than TCE. Here, the authors found that mitochondria-related transcriptional pathways are strongly affected, in dose-response manner, in both liver and kidney by PCE but not TCE [Zhou *et al*., 2017]. Their results were supported by prior observations showing that PCE had a much stronger effect on uncoupling mitochondrial oxidative phosphorylation than TCE [Ogata and Hasegawa, 1981]. Such mitochondrial effects may be mediated through decreased electron flow at the susceptible portion in the mitochondrial inner membrane [Miyazaki and Takano, 1983]. As stated above, mitochondrial toxicity is a critical mechanism of PD. Moreover, both PCE and TCE have been tested together for inhibition of mitochondrial respiration (Figure 10), where PCE (relative to TCE) was both more lipophilic and more potent.

However, Zhou *et al*. (2017) did not find any effect of TCE on mitochondria.

Plaintiffs' experts (see for example, De Miranda [2024]; Costa [2024]) state that the MoA of PD involves a very specific effect on dopaminergic neuron mitochondria, *i.e*., inhibition of mitochondrial complex I. Mitochondrial uncoupling, which is defined as a loss of the link between mitochondrial oxygen consumption and ATP production caused by loss of mitochondrial membrane potential (Lehman-McKeeman, 2019), is not implicated in the pathology of PD, nor does it involve complex I inhibition. Therefore, the fact that Ogata and Hasegawa (1981) report mitochondrial uncoupling does not provide evidence that PCE can cause PD.

Miyazaki and Takano (1983) concluded that "tetrachloroethylene does not represent a specific inhibitor of the particular carrier but decreased the electron flow at the susceptible portion in the mitochondrial inner membrane [*sic*]." That is, the authors concluded that PCE does not inhibit a specific electron transport chain complex (complex I or otherwise).

Finally, Fiorucci *et al*. (1988) did not evaluate PCE and TCE. The authors evaluated the compound 1,1,1-trichloroethane, not TCE.

Collectively, Dr. Cannon's statements indicate a lack of understanding of the scientific literature, and none of the studies he cites support his conclusion that PCE is a cause of PD.

11.5.7 Coherence

Plaintiffs' experts' conclusions regarding coherence are not supported by the evidence.

Plaintiffs' experts generally agree that human and experimental evidence show that TCE can cause PD. As discussed throughout this report, neither the human nor the experimental evidence supports causation.

11.5.8 Experiment

Some Plaintiffs' experts misinterpret what Bradford Hill (1965) meant by experiment.

By experiment, Bradford Hill (1965) meant that 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. This is specific to human experiments (*e.g*., randomized control trials), not animals.

Drs. Boehme and Bird both acknowledge this definition of experiment, but Dr. Bird concludes that since it would be unethical to dose people with TCE, experimental studies in animals and observational epidemiology studies in humans demonstrate "the experimentation criterion has also been met." Dr. Miller comes to a similar conclusion. Drs. Boehme, Cannon, Costa, and Freeman all incorrectly discuss laboratory studies in the context of this consideration. The fact that conducting human experiments is unethical does not mean that animal studies address the Bradford Hill consideration of experiment.

Setting aside the fact that the observational epidemiology and experimental animal studies that have evaluated TCE, PCE, benzene, and vinyl chloride do not support causal associations with PD, evidence from these studies has no bearing on whether this Bradford Hill (1965) consideration is met.

11.5.9 Analogy

11.5.9.1 TCE and PCE Physicochemical Properties

Plaintiffs' experts do not discuss physicochemical differences between TCE and PCE.

Dr. Boehme (2024), Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), Dr. Costa (2024), Dr. Freeman (2024), and Dr. Bird (2024) claim that PCE and TCE are analogous, citing shared cellular mechanisms that are associated with PD-like symptoms in animal models. However, Dr. Bird (2024) correctly states, "The closely related chemical structure of chlorinated ethenes, specifically the three present at Camp Lejeune, does not mean they cause the same biological effects."

There are fundamental differences between physiochemical properties, metabolism, and MoA of TCE and PCE, which results in distinct toxicological profiles. The additional chlorine atom in PCE results in altered chemical reactivity and subsequent biological response. That is, PCE is more dense, less soluble, and less volatile compared to TCE (ATSDR, 2019a,b).

Many other chemicals that only differ by one atom have vastly different toxicological profiles. Examples include water (H_2O) and hydrogen peroxide (H_2O_2), and carbon dioxide (CO_2) and carbon monoxide (CO). H_2O_2 and CO are inherently reactive and disrupt normal cellular function, while H_2O and CO_2 are vital for maintaining physiological homeostasis. Water is essential for all life while hydrogen peroxide is a corrosive oxidizing agent that is induces central nervous system damage, cardiorespiratory arrest, and gastrointestinal disruption, among other adverse effects upon ingestion (Watt *et al*., 2004). Carbon monoxide is a potent toxicant that causes tissue hypoxia and targets the cardiovascular system, lungs, blood, central nervous system at low concentrations (CDC, 2019a,b).

11.5.9.2 TCE and PCE Metabolism

Most of these Plaintiffs' experts do not acknowledge metabolic differences between PCE and TCE.

Dr. Cannon (2024) states, "PCE and TCE overlap with respect to PD extends beyond Analogy, where biological plausibility is supported by overlapping and metabolic pathway metabolites. Here, specifically, mitochondrial toxicants and mitochondrial toxicity (important primary PD pathogenic mechanism) are expected products. Again, serving as further evidence that PCE neurotoxicity to a degree of reasonable scientific certainty is expected to be highly similar to TCE." This conclusion is contradicted by the metabolic differences that inform the toxicity profiles of TCE and PCE.

Dr. Cannon (2024) correctly states that "it is worth noting that there are considerable differences in metabolism across species, where humans may have different metabolic flux." TCE undergoes oxidative metabolism producing several compounds linked to liver and kidney toxicity at sufficient doses. Trichloroethanol (TCOH), one of the major oxidative metabolites of TCE, has been implicated in kidney injury though inhibition of formic acid at high doses. The accumulation of TCOH in kidney tissue is thought to contribute to the higher incidence of kidney toxicity observed with TCE compared to PCE (Luo *et al*., 2018a). Dr. Costa (2024) states, "Second, PCE, like TCE, can be metabolized to the mitochondrial neurotoxicant TaClo (Riederer *et al*., 2002) which is believed to be the ultimate toxicant in TCE dopaminergic neurotoxicity."

As discussed in Section 6.3, this is incorrect. US EPA (2011a) concluded that (1) there is insufficient evidence to determine whether TaClo contributes to PD-like symptoms, and (2) that a majority of findings from toxicity studies are inconsistent and suggest that TaClo does not have specificity for the dopaminergic system and is not selectively toxic to dopaminergic neurons (Storch *et al*., 2006; Lock *et al*., 2013). Overall, even if evidence was sufficient to support TCE as a cause of PD, which it is not, differences between TCE and PCE metabolism indicate that any evidence regarding TCE is not informative with respect to PCE.

11.5.9.4 Basis of TCE and PCE Risk Criteria

Plaintiffs' experts do not acknowledge differences between the basis of risk criteria for cancer and non-cancer endpoints for TCE and PCE.

Regulatory agencies have concluded that TCE is a known human carcinogen based on the occurrence of kidney cancer (US EPA, 2011a; IARC, 2014b; NTP, 2015b; ATSDR 2019a). Conversely, no regulatory agencies or scientific organizations have concluded that PCE is a known human carcinogen and instead classified PCE as "likely" (US EPA, 2012, 2020b), "probably" (IARC, 2014a; ATSDR 2019b), or "reasonably anticipated" (NTP, 2016) to be carcinogenic in humans based on bladder cancer, not kidney cancer. For PCE noncancer effects, the most sensitive endpoint used for the derivation of an oral reference

dose (RfD) included effects on cognitive and visuospatial function and color perception (US EPA, 2012; Cavalleri *et al*., 1994; Echeverria *et al*., 1995). For TCE noncancer effects, the most sensitive endpoint used for the oral RfD derivation was immune and developmental effects (US EPA, 2011a; Keil *et al*., 2009; Johnson *et al*., 2003).

Although cancer risk has no bearing on PD risk, this further demonstrates how regulatory agencies confirm that TCE and PCE are chemically and toxicologically distinct. These distinctions highlight that PCE and TCE are not analogous.

11.5.9.5 MPTP

TCE and MPTP are distinct substances with differing toxicological profiles.

According to Dr. Bird (2024), "While the exact mechanisms of action of TCE on these neurons is not known, they were able to show that TCE inhibits mitochondrial complex I, as seen with other parkinsonian mimetics, such as MPTP toxicity." While MPTP and TCE both inhibit mitochondrial complex I, their toxicological effects and mechanisms of action differ substantially, particularly regarding PD.

Numerous chemicals inhibit mitochondrial complex I but do not induce Parkinson's. For example, metformin, the most widely prescribed diabetes medication, inhibits mitochondrial complex I and does not cause PD (Fontaine, 2018). MPTP induces Parkinson-like symptoms through metabolism in the brain into MPP+, a compound selectively toxic to dopaminergic neurons in the *substantia nigr*a (Snyder and D'Amato, 1986). MPTP's specificity for dopaminergic neurons in the *substantia nigra*, combined with its potent and acute neurotoxic effects, makes it a direct inducer of PD-like pathology and is frequently used as a positive control in laboratory studies to induce Parkinson's-like symptoms in experimental animals. In contrast, TCE's effects on dopaminergic neurons are far less pronounced compared to MPTP. These differences underscore that TCE does not induce Parkinson's-like symptoms in the same way as MPTP.

11.5.9.6 Other Substances

Plaintiffs' experts do not provide evidence that other substances cause PD or are analogous to TCE or PCE.

Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), and Dr. Costa (2024) claim that TCE and PCE are mechanistically analogous to pesticides, such a glyphosate or rotenone, that can cause PD. These experts state that these pesticides can produce molecular effects in experimental animals similar to those observed in human PD, but the studies provide no evidence that these pesticides can actually cause PD in humans. Regardless, they interact with biological systems in fundamentally different ways than TCE due to their distinct chemical structures and metabolic pathways (Richardson *et al*. 2005; Tieu 2011; Lock and Wilks, 2010).

Rotenone, for example, is a compound with a multi-ring structure, which allows it to specifically target and inhibit mitochondrial complex I, disrupting the electron transport chain and leading to cellular energy depletion (Tieu, 2011). In contrast, TCE is a simple, three carbon compound with three chlorine atoms that can interact with various biological systems (US EPA, 2011). The distinct chemical structures of these compounds also influence their metabolic pathways. For example, glyphosate is excreted primarily unchanged *via* the feces, rotenone is metabolized primarily in the liver by CYP3A4 and CYP2C19 enzymes, and TCE is metabolized primarily in the liver by CYP2E1, with different reactive metabolites being formed

(US EPA, 2011, 2015; Caboni *et al*., 2004). These illustrative examples demonstrate how the mechanisms of glyphosate, rotenone, and TCE are fundamentally different from one another.

11.6 Exposures

11.6.1 VOC Concentrations at Camp Lejeune

Exceedance of MCLs does not provide evidence for an increased risk of PD.

According to US EPA (2024c), the MCL is "[t]he highest level of a contaminant that is allowed in drinking water. MCLs are set as close to… MCLGs… as feasible using the best available treatment technology and taking cost into consideration. MCLs are enforceable standards." Maximum contaminant level goals (MCLGs) are "[t]he level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs for carcinogens are zero, and MCLs are set as close to MCLGs as possible, considering laboratory analytical sensitivity and the cost of chemical analysis. MCLGs allow for a margin of safety and are non-enforceable public health goals" (US EPA, 2024c). However, exceedance of an MCL does indicate an increased risk of any health condition generally, or PD specifically.

Drs. Bird (2024), Boehme (2024), Costa (2024), Freeman (2024), and Miller (2024) indicate that TCE, PCE, benzene, and vinyl chloride were present in drinking water at Camp Lejeune at concentrations exceeding their respective MCLs (*i.e*., 5 µg/L for TCE, PCE, and benzene and 2 µg/L for vinyl chloride) during a certain time period. Only Dr. Bird (2024) notes that he does "not opine on issues such as reliability of historical evidence for TCE or PCE water concentrations at the base or of ATSDR water modeling reconstruction of past contaminant levels in the water," although this is true for all these Plaintiffs' experts. No expert estimates how much water any individual consumed (*e.g*., in drinking water or while showering or doing laundry). Importantly, none of these experts acknowledge that none of the MCLs for these VOCs are based on PD (US EPA, 2024c). As such, exceedance of any of these MCLs does not provide any evidence for an increased risk of PD.

11.6.2 TCE Exposure Calculation

Dr. Miller's exposure calculation is misleading.

As discussed in Section 5.6, 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.

Dr. Miller (2024) estimates TCE exposures at Camp Lejeune in a similar manner. He assumes that the median TCE contamination on base was 366 ug/L. This is the median concentration modeled in water supplied by the Hadnot Point system between 1975-1985 (the time period of the highest TCE

concentrations) (Bove *et al*. 2014a) but does not represent median concentrations at other times or from other water sources on base. Dr. Miller (2024) also assumes people on base each drank 3 L water per day (not 2 L), stating that this is at the lower end of 3-6 L/day people drank on base each day, again providing no evidence or rationale for this divergence from the standard 2 L/day assumption. He states that oral consumption of contaminated water accounts for approximately half of the total dose of TCE and, to be conservative, he assumes that vapor and dermal exposures increase dose by two-thirds. To account for this, he assumes people on base drank 5 L of water per day (*vs.* 4 L/day as assumed by NRC [2009]), resulting in a daily dose of 5 L x 366 µg/L = 1,830 µg/day, or 1,830 µg/day x 90 days = 164.7 mg TCE over 90 days.

In addition to his many assumptions, Dr. Miller (2024) inappropriately expresses dose in mg/day instead of mg/kg-day, which is generally accepted in the field of toxicology (US EPA, 1989a). Dividing by 70 kg results in an exposure of (1,830 ug/day)/(70 kg) = 0.026 mg/kg-day; dividing by 80 kg results in an exposure of 0.023 mg/kg-day.[22] Furthermore, multiplying by 90 days for a cumulative dose is non-sensical in this context. Accepted practice is to compare dose in mg/kg-day to reference values or doses in experimental studies in these same units (US EPA, 1989a).

Dr. Miller (2024) states, "The 2023 Goldman paper concluded the PD incidence was higher in personnel who spent at least three months at Camp Lejeune, therefore, the dose of TCE that they received over a three-month period must be sufficient to cause the increased incidence." As discussed in detail in Section 5, this study does not provide evidence for a causal association at this cumulative dose or by any other dose metric. Regardless, the amount of TCE to which each individual was exposed varied over time and all 90-day doses were not the same. For example, some individuals were not exposed to TCE at all, while others may have been at Camp Lejeune during the peak period of water contamination. Even during time periods with peak contamination, TCE exposures varied between individuals at Camp Lejeune based on individual behaviors (*e.g*., showering and laundry habits), water ingestion, and water source(s).

It is notable that the calculated dose of 0.023-026 mg/kg-day is about 7,500 to 43,500 times lower than the doses in toxicology studies at which biological effects have been observed (200-1,000 mg/kg-day), although these effects (*e.g*., dopaminergic neuron loss) are not of sufficient magnitude to result in PD in humans (see Section 6.2).

11.6.3 Route of Exposure

Dr. De Miranda's calculation of the potency of inhaled TCE is wrong.

Dr. De Miranda (2024) claims that inhaled TCE is 500 times more potent (toxic) than ingested TCE (and this is also noted by Dr. Miller). However, this claim in not supported. Dr. De Miranda bases the claim on increased neurodegeneration observed in a 50-ppm inhalation rat study compared to that observed in a 200 mg/kg oral rat study, both performed in her laboratory (Adamson *et al*., 2023; De Miranda *et al*., 2021). However, this comparison is inappropriate because the exposure durations for the two studies differed substantially. In Adamson *et al*. (2023), the authors acknowledge this, stating that the greater dopaminergic neuron loss observed in the inhalation study (50%) compared to the oral study (35%) may have been due to the increased exposure duration in the inhalation study (8 weeks) compared to that of the oral study (6 weeks).

Dr. De Miranda's claim that inhaled TCE is 500 times more potent than ingested TCE is also based on a faulty calculation and incorrect assumptions. Dr. De Miranda says she converted an ingestion dose of 200

[22] Although NRC (2009) used an adult body weight of 70 kg, US EPA (2011b) assumes the mean adult body weight for males and females is 80 kg.

mg/kg-body weight TCE in rats to 136.986301 mg/L air by dividing the TCE concentration by the density of TCE (1.46 g/cm^3). However, because the dose of TCE is in mg of TCE per kg of body weight, dividing by the density does not result in a number with any meaning.[23] She then converts an air concentration of 50 ppm TCE to 0.27328285 mg/L air and notes that the ratio of 136.986301 mg/L air to 0.27328285 mg/L is 501.26196. This ratio is meaningless, as the conversion of the oral 200 mg/kg-body weight dose to mg/L air is incorrect. Dr. De Miranda (2024) further claims that a 200 mg/kg-body weight TCE dose in rats is equivalent to 25,063.10 ppm. Again, this is nonsensical, as oral doses per body weight are not compared to ppm concentrations in air.

In order to compare the potency or toxicity of a chemical among studies involving different exposure routes, estimates of internal tissue doses are necessary. The only reliable way extrapolate toxicity across routes is using chemical- and species-specific physiologically based pharmacokinetic (PBPK) models that can estimate internal doses from different exposure routes (oral, inhalation, dermal).

This faulty concept that inhaled TCE is 500 times more potent than ingested TCE is also claimed by Dr. Miller in his report, but is inconsistent with Dr. Miller's suggestion that "if one uses the lower end of the estimate [of liquid consumption] of 3 liters per day and assumes other sources represent an additional two-thirds (67%) exposure then one can use an oral dose of 5 liters consumption/day as a proxy to represent to total exposure from combined routes (oral, vapor/inhalation, and dermal, 3 liters x 1.67 = 5 liters)." That is, Dr. Miller claims in one place that inhalation exposure is 500 times more potent than ingestion, but only considers adding 2 L to his total exposure scenario to account for inhalation and dermal exposure. If inhalation to TCE is 500 times more potent than ingestion of TCE, one would have to add 1,500 L to the total exposure scenario.

11.7 Benzene

There is no evidence that benzene can cause PD.

Dr. Bird (2024), Dr. Freeman (2024), Dr. De Miranda (2024) and Dr. Cannon (2024) briefly discuss benzene and PD, while Dr. Boehme, Dr. Miller, and Dr. Costa do not discuss benzene at all. Dr. Cannon (2024) states, "Benzene is in a different chemical class and not linked to PD." This is consistent with the conclusions of Dr. Freeman (2024), who states that "there is below equipoise evidence for a causal relationship between benzene exposure associated with drinking water at Camp Lejeune and Parkinson's disease due to the paucity of epidemiologic and mechanistic studies." In contrast, Dr. Bird (2024) states, "It is also my opinion that the levels of exposure to these chemicals at Camp Lejeune [TCE, PCE, benzene, and vinyl chloride] are hazardous to humans, and specifically as likely as not cause Parkinson's Disease."

Dr. Bird's conclusions regarding benzene and PD are not only inconsistent with other Plaintiffs' experts, but also regulatory agencies such as the US EPA and ATSDR, which conducted in-depth reviews but do not discuss an association between benzene and PD. No toxicity studies have evaluated benzene exposure and PD, as discussed in Section 8.2. There is no evidence to support a causal association between benzene and PD.

[23] Animals are dosed in mg of chemical per kg of body weight. This concept is analogous to doses of medicine being smaller for children than adults. For children to ingest the same amount as adults, they ingest a smaller amount to account for their smaller body weight. It would be nonsensical to convert an oral dose of a drug based on a person's body weight to a number divided by liters or gallons of air based on the density of the drug. That is essentially what Dr. De Miranda has done.

11.8 Vinyl Chloride

There is no evidence that vinyl chloride can cause PD.

Dr. Cannon (2024), Dr. Freeman (2024), and Dr. Bird (2024) briefly discuss vinyl chloride and PD. Dr. Bird (2024) concludes that "these water contaminants [TCE, PCE, vinyl chloride, and benzene] have been shown to cause adverse health effects, including Parkinson's Disease, in occupational studies, environmental studies outside of Camp Lejeune, and specifically in Marines and civilians who were based at Camp Lejeune, especially given the reduced standard at issue in this litigation, an as likely or not standard, or equipoise." Dr. Boehme (2024) does not address vinyl chloride specifically, but concludes that "it is at least as likely as not that exposure to the water at Camp Lejeune, contaminated with…other volatile organic compounds, can cause Parkinson's Disease."

The conclusions of Dr. Bird (2024) and Dr. Boehme (2024) contradict those of Dr. Freeman (2024), that "there is below equipoise evidence for a causal relationship between vinyl chloride exposure associated with drinking water at Camp Lejeune and PD due to the paucity of epidemiologic and mechanistic studies." They are also not consistent with conclusions of US EPA or ATSDR, neither of which conclude that vinyl chloride can cause PD. As discussed in Section 9.1, there are only two epidemiology studies that assess exposures to vinyl chloride and PD, both at Camp Lejeune. In both studies, participants were potentially exposed to several chemicals in addition to vinyl chloride, making it impossible to assess the specific relationship between vinyl chloride and PD. As discussed in Section 9.2, there are no experimental studies evaluating vinyl chloride exposure and PD, and no MoAs have been investigated. Dr. Cannon (2024) acknowledges in his report that vinyl chloride has received little research attention on PD.

11.9 Mixtures

Combined environmental exposures to TCE, PCE, benzene, and vinyl chloride would not result in a higher risk of PD.

Plaintiffs' experts Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), Dr. Freeman (2024), and Dr. Bird (2024) make broad statements indicating that combined exposures to TCE, PCE, and other VOCs, including benzene and vinyl chloride, would result in more neurotoxicity than exposure to one solvent in isolation. Dr. Bird (2024) concludes that "the science published in the area to date is compelling and supports a qualitative conclusion (particularly under an 'equipoise' or 'as likely as not' standard) that Camp Lejeune Plaintiffs were exposed by multiple routes of exposure to multiple chemicals with (as likely as not) additive if not multiplicative effect." Similarly, Dr. De Miranda (2024) concludes that "published literature on solvent toxicity suggests that additive effects would be predicted from combined exposures, as different solvents induce damage in specific pathological pathways that could render cells and tissue more vulnerable."

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 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 interactions 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, 1989b, 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 any indication of whether combined effects would occur in animals of other species, in animals of other strains of the same species, or in subjects of different ages (Mauderly and Samet, 2008). 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, 2008).

Scientific evidence does not demonstrate that TCE, PCE, vinyl chloride, or benzene individually can cause PD (discussed in Sections 5-9). 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 cause PD.

Dr. De Miranda (2024), Dr. Miller (2024), Dr. Cannon (2024), Dr. Freeman (2024), and Dr. Bird (2024) draw conclusions regarding combined effects from TCE, PCE, benzene, and vinyl chloride without considering that evidence doesn't support any of these chemicals as causal or that each chemical acts on different molecular pathways and cell types, and that effects vary by dose, species/strain, and age-related differences.

11.10 US EPA's 2024 TCE and PCE Rulings

Dr. Cannon (2025) cites US EPA final rules for TCE and PCE (US EPA 2024a,b) and a related news release (US EPA 2024d) in his Supplemental report, claiming that, because these rules indicate that TCE and PCE can cause neurotoxicity, they can cause PD. Dr. Cannon pastes every sentence that mentions neurotoxicity in both rules in his supplemental report, and states, "EPA's ruling rational is inclusive of overall neurotoxicity and, specifically PD risk."

US EPA (2024a,b) did not state or imply that evidence for neurotoxicity indicates that TCE and PCE can cause every type of neurotoxicity or PD specifically. There are many types of neurotoxicity with very different MoAs. PD occurs when there is a significant loss of dopaminergic neurons. Evidence for neurotoxicity that does not involve dopaminergic neuron loss provides no evidence for PD.

The final rule for PCE does not discuss PD specifically. The final rule for TCE mentions PD only once. The rule refers to an association with PD, citing US EPA (2020a). US EPA (2020a) stated that "several newer epidemiological studies have found an association between TCE exposure and neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (Bove *et al.,* 2014a) and Parkinson's disease (Bove *et al.*, 2014b; Goldman *et al.*, 2012)." This risk evaluation provided no further discussion of TCE and PD epidemiology studies and did not indicate that these associations were likely causal. US EPA (2020a) also did not discuss any animal or mechanistic studies (including studies that evaluated TaClo) that investigated TCE and PD. US EPA did not conclude that either TCE or PCE is a cause of PD (2024a,b).

Dr. Cannon (2025) also states:

> These determinations further support the overall scientific conclusion from the General Causation Report that: Tetrachloroethylene (PCE) is at least as likely as not a cause of PD. The TCE ruling specifically bolsters the following scientific evidence in the General Causation Report that led to the overall conclusion: Structural similarity and structural activity relationships to trichloroethylene (TCE), which is a known PD risk factor based upon collective epidemiological and neurotoxicological data. There is also a lack of scientific support for the alternate hypothesis that 1 additional chlorine atom and 1 less hydrogen atom (PCE *vs* TCE) would be protective in preventing PD risk. EPA's ruling rational is inclusive of overall neurotoxicity and, specifically PD risk. Given the extensive scientific documentation in the General Causation Report that PCE neurotoxicity would be expected to be similar to TCE, with respect to PD, EPA's ruling for TCE further supports plausibility of PCE induced PD relevant risk.

As discussed in detail in Section 11.5.9, there are fundamental differences between physiochemical properties, metabolism, and MoA of TCE and PCE, which results in distinct toxicological profiles. The

additional chlorine atom in PCE results in altered chemical reactivity and subsequent biological response. PCE is more dense, less soluble, and less volatile than TCE (ATSDR, 2019a,b). Thus, even if evidence supported TCE as a cause of PD, which it does not, it would not be relevant to PCE.

11.11 Conclusions

Seven of the Plaintiffs' experts opine that exposures to TCE, PCE, benzene, and vinyl chloride are as least as likely as not to cause PD generally and at Camp Lejeune. These experts do not conduct objective, rigorous, systematic evaluations of the scientific evidence that include an evaluation of study quality and the impact of study quality on the interpretation of results. As such, their discussions of the scientific evidence do not support their conclusions that there is sufficient evidence of causal associations or that causal associations are as least as likely as not.

12 Conclusions

Based on a review of the relevant epidemiology and toxicology literature, and reviews by government and scientific agencies, I conclude to a reasonable degree of scientific certainty:

- Epidemiology studies of Marines and Navy personnel stationed at Camp Lejeune and civilian workers on base do not provide evidence for an association between working or living at Camp Lejeune or exposure to TCE, PCE, benzene, or vinyl chloride in drinking water on base and PD incidence or mortality.
- These and most other epidemiology studies of TCE, PCE, benzene, and vinyl chloride exposure and PD do not provide evidence of associations in most analyses and have several methodological limitations, including a lack of direct measurements of individual-level exposures. As such, they do not provide evidence for causal associations.
- No laboratory animal model exactly mimics the etiology, progression, and pathology of human PD. While subchronic- and subacute-duration experimental animal studies have reported some PD-associated pathological or behavioral effects in rats and mice exposed to very high doses of TCE, the exposure conditions are not relevant to human exposures, and the magnitudes of effects (specifically on dopamine levels and dopaminergic neuron loss in the SNpc) were below those necessary to produce clinical signs of PD in humans. Also, some behavioral effects were not consistent within or across studies.
- PD has not been evaluated in PCE toxicity studies. Suggestions that a common metabolite of TCE and PCE may cause PD is not supported by the available evidence.
- ATSDR (2017a), which was written by one person over a period of 6 weeks concluded that "epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above," but "there is equipoise and above evidence for causation for TCE and Parkinson disease" based on "strong supporting mechanistic evidence." This conclusion is inconsistent with all other agency reviews, including the ATSDR Toxicological Profile, none of which concluded that TCE is a known cause of PD. No agency concluded that PCE, benzene, or vinyl chloride causes PD.
- No epidemiology or animal studies have evaluated specific exposures to benzene, vinyl chloride, or *trans*-1,2- DCE and PD. No scientific or regulatory agency has addressed whether any are a known cause of PD. There is no evidence that benzene, vinyl chloride, or *trans*-1,2-DCE exposure can cause PD.
- Seven Plaintiffs' experts opine that exposures to TCE, PCE, benzene, and vinyl chloride are as least as likely as not to cause PD generally and at Camp Lejeune. These experts do not conduct objective, rigorous, systematic evaluations of the scientific evidence that include an evaluation of study quality and the impact of study quality on the interpretation of results. As such, their discussions of the scientific evidence do not support their conclusions that there is sufficient evidence of causal associations or that causal associations are as least as likely as not.

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 PD. 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 PD

A.1.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated trichloroethylene (TCE) and Parkinson's disease (PD) for various purposes (US EPA, 2011a, 2020b; ATSDR, 2017, 2019a; NTP, 2015a). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For TCE and PD, the searches identified epidemiology, animal carcinogenicity, and mode-of action studies published from January 1, 2016, to June 18, 2024.

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.

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 ("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease") 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])) NOT (mice OR mouse OR rat OR rats OR rodent)

A.1.2.2 Animal Carcinogenicity

(("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 toxicology OR toxic* OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotoxicity 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*) 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.1.2.3 Mode of Action

("Trichloroethylene"[Mesh] OR trichloroethylene OR TCE[ti]) OR (79-01-06[EC/RN Number]) OR (1,1-Dichloro-2-chloroethylene[tiab] OR 1-Chloro-2,2-dichloroethylene[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR Dow-Tri[tiab] OR Dukeron[tiab] OR (Ethene[tiab] AND trichloro[tiab]) OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab] AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR Fleck-Flip[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR TRIC[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR Tri-Plus[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab]) AND ("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*) AND (mechanistic* OR mechanism* OR "mode of action") NOT (mice OR mouse OR rats OR rat OR rodent)

A.1.3 Scopus Search Terms

A.1.3.1 Epidemiology

(TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson) 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 and Mode of Action

(TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson) 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.2 Perchloroethylene and PD

A.2.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated perchloroethylene (PCE) and PD for various purposes (US EPA, 2012, 2020b; ATSDR, 2017, 2019b). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For PCE and PD, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016, to June 18, 2024.

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.

A.2.2 PubMed Search Terms

A.2.2.1 Epidemiology

((((("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0])) AND ("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease") 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])) NOT (mice OR mouse OR rat OR rats OR rodent)

A.2.2.2 Animal Carcinogenicity and Mode of Action and Mode of Action

(("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene" 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 of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh])) OR ((mechanistic* OR mechanism* OR "mode of action"))) AND (("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease" OR parkinson*))

A.2.3 Scopus Search Terms

A.2.3.1 Epidemiology

(TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson*) 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 ("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 NOT TITLE-ABS (mice OR mouse OR rat OR rats OR rodent OR rodents) AND (LIMIT-TO (LANGUAGE , "English"))

A.2.3.2 Animal Carcinogenicity and Mode of Action and Mode of Action

(TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) AND ((TITLE-ABS-KEY (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 SRCTITLE (toxciol*)) OR (TITLE-ABS-KEY (mechanistic* OR mechanism* OR "mode of action"))) AND (TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson*))

A.3 Benzene and PD

A.3.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated benzene and PD for various purposes (US EPA, 2002; ATSDR, 2007b, 2015, 2017). I then conducted literature searches using PubMed and Scopus. For benzene and PD, the searches identified all epidemiology, animal carcinogenicity, and mode-of-action studies published through June 18, 2024.

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.

A.3.2 PubMed Search Terms

A.3.2.1 Epidemiology

("Benzene"[Mesh] OR "benzene"[Title/Abstract]) AND ("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease" OR parkinson*) 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 OR dog OR dogs OR treatment)

A.3.2.2 Animal Carcinogenicity and Mode of Action and Mode of Action

((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"))) AND (("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease" OR parkinson*))) NOT parkinson[Author])

A.3.3 Scopus Search Terms

A.3.3.1 Epidemiology

(TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson*) 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*)) AND (KEY (benzene) OR TITLE (benzene)) AND NOT TITLE-ABS (mice OR mouse OR rat OR rats OR rodent OR rodents OR vitro OR vivo) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (EXACTKEYWORD , "Nonhuman"))

A.3.3.2 Animal Carcinogenicity and Mode of Action and Mode of Action

(KEY (benzene) OR TITLE (benzene)) 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*)) AND (TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson*)) AND NOT TITLE-ABS-KEY (ethnopharmacolog* OR ethnobotany OR treatment) AND (LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "BIOC"))

A.4 Vinyl Chloride and PD

A.4.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated vinyl chloride and PD for various purposes (US EPA, 2000a,b; ATSDR, 2006, 2016, 2017). I then conducted literature searches using PubMed and Scopus. For vinyl chloride and PD, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published through June 18, 2024.

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.

A.4.2 PubMed Search Terms

A.4.2.1 Epidemiology

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

A.4.2.2 Animal Carcinogenicity and Mode of Action and Mode of Action

((("Vinyl Chloride"[Mesh] OR "Vinyl chloride" OR Chloroethene OR chloroethylene OR "1-chloroethylene"[Title/Abstract:~0] OR "ethylene monochloride" OR "monovinyl chloride" OR monochloroethene OR monochloroethylene OR Trovidur OR 75-01-4[EC/RN Number])) AND (((toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically

induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh])) OR ((mechanistic* OR mechanism* OR "mode of action"))) AND (("Parkinson Disease"[Mesh] OR "Parkinson Disease" OR "Parkinson's Disease" OR parkinson*)))

A.4.3 Scopus Search Terms

A.4.3.1 Epidemiology

(TITLE-ABS-KEY ("parkinson disease" OR {Parkinson disease} OR parkinson*) 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*)) 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 NOT TITLE-ABS (mice OR mouse OR rat OR rats OR rodent OR rodents OR vitro OR vivo) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (EXACTKEYWORD , "Nonhuman"))

A.4.3.2 Animal Carcinogenicity and Mode of Action and Mode of Action

(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*)) AND (TITLE-ABS-KEY ("parkinson disease" OR {Parkinson's disease} OR parkinson*)) AND NOT TITLE-ABS-KEY (treatment)

Attachment B

Camp Lejeune Epidemiology Studies

List of Tables

Table B.1 Camp Lejeune Cohort Study Characteristics

Study	Study Population				Exposure Characterization		Cancer Outcome		
	Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Ascertainment	Follow-up Period
Bove *et al.* (2014a)[a]	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	SSA and NDI	1979-2008
ATSDR (2018b)[c]	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	Stationed or employed at base, or 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	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012
Goldman *et al.* (2023)	Marines & Navy personnel at CL and CP	B	CL: 59.6[e] CP: 59.8[e]	CL: 84,824 CP: 73,298	1975-1985	Stationed at base for at least 3 mos	Inc	VHA, CDWP[f] files, Medicare files, and medical records	1997-2021

Study	Study Population				Exposure Characterization		Cancer Outcome		
	Population	Sex	Age (yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Ascertainment	Follow-up Period
Bove *et al.* (2024a)	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: 232,0126 Began Active Duty 1975-1985[g] 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	SSA Data for Epidemiological Researchers and NDI	1979-2018

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CDWP = Corporate Data Warehouse Outpatient, Inpatient, and Community Care; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; Mo = Month; Mort = Mortality; NDI = National Death Index; SSA = Social Security Administration; VHA = Veterans Health Administration; Yr = Year.
$\bar{x}$ = Mean.
(a) Bove *et al.* (2014b) evaluated exposures at CL and health outcomes in Marines and Navy personnel using similar methods to those used in Bove *et al.* (2014a). There were < 5 cases of PD observed so they did not evaluate associations in analyses of Marines and Navy personnel.
(b) Median age from start to end of follow-up (Bove *et al.*, 2014a).
(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).
(e) Mean age at the end of follow-up (Goldman *et al.*, 2023).
(f) CDWP consists of care in the community paid for by VHA (Goldman *et al.*, 2023).

(g) 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 PD Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Bove *et al.* (2014a)	US general population	Mort	SMR	**CL Civilian Employees**					Age, sex, race, and calendar period
				All	5	2.28	2.19 (0.71-5.11)	–	
	CP civilian employees		HR	All (10-yr lag)	5	–	3.13 (0.76-12.86)		Age, sex, race, blue- or white-collar occupation, and education
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					–
				All	78	–	0.89 (0.51-1.55)	–	
	CP civilian employees			**CL Civilian Employees**					Sex
				All	20	–	**3.11 (1.16-8.32)**	–	
Goldman *et al.* (2023)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age, sex, and race and ethnicity[d]
				All[b]	279[c]	–	**1.70 (1.39-2.07)**	–	
Bove *et al.* (2024a)[e,f]	US general population	Mort	SMR	**CL Marines & Navy Personnel**					Age, sex, race, and calendar period
				Began active duty between 1975-1985	15	–	1.47 (0.73-2.21)	–	
				All	64		1.01 (0.76-1.26)		
	CP Marines & Navy personnel		RR	Began active duty between 1975-1985	15		2.00 (0.85-4.73)		Age, sex, and race
				All	64		1.06 (0.75-1.49)		
			HR	Began active duty between 1975-1985	15		2.05 (0.86-4.87)		Age, sex, race, rank, and education level
				All	64		1.29 (0.92-1.82)		
				Began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	2.07 (0.62-6.95)	–	
				Medium (> 2-7)			2.63 (0.91-7.66)		
				High (> 7)			1.59 (0.51-4.96)		
	US general population		SMR	**CL Civilian Employees**					Age, sex, race, and calendar period
	CP civilian employees		RR	All	30	–	1.34 (0.86-1.82)	–	Age, sex, and race
			HR		30		1.15 (0.68-1.93)		Age, sex, race, blue collar work, and education level
					30		1.21 (0.72-2.04)		
				Duration of employment (quarter yrs)					
				Low (1-5)	–	–	0.23 (0.03-1.69)	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
				Medium (6-22)			1.19 (0.55-2.54)		
				High (23-53)			1.60 (0.88-2.90)		

Notes:

ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; COPD = Chronic Obstructive Pulmonary Disease; CP = Camp Pendleton; DLB = Dementia with Lewy Bodies; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; PD = Parkinson's Disease; RR = Relative Risk; SMR = Standardized Mortality Ratio; US = United States; VHA = Veterans Health Administration; Yr = Year.

– = 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) In a sensitivity analysis restricted to those diagnosed with PD before January 13, 2017 (*i.e.*, the date of the government ruling on presumptive service connection for eight diseases associated with the contaminated water), this relationship was no longer statistically significant (OR = 1.28, 95% CI: 1.00-1.64). Sensitivity analyses that included only participants who were active VHA users prior to PD diagnosis, had "probable" PD, or that considered DLB diagnoses in addition to PD diagnoses did not substantially change the results. No statistically significant associations were found for other forms of neurodegenerative parkinsonisms.

(c) Includes both possible and probable cases (Goldman *et al.*, 2023).

(d) Adding smoking status (*i.e.*, ever/never) or military rank (*i.e.*, officer/enlisted) to the model had minimal impact, though smoking status was unknown for 27.6% of the cohort (Goldman *et al.*, 2023).

(e) Bove *et al.* (2024a) also ran analyses based on contributing causes, which I do not report here.

(f) Bove *et al.* (2024a) conducted a quantitative bias analysis to evaluate the impact of exposure misclassification and unmeasured confounding from smoking. Based on differences in risk of COPD, they assumed a 6% smoking prevalence difference between Camp Lejeune and Camp Pendleton Marines and Navy personnel and a 4% difference between civilians at Camp Lejeune and Camp Pendleton. Using this to adjust for smoking, they reported an HR increase of ≤ 6.8% in Marines and Navy personnel and an increase of ≤ 4.1% in civilians. When considering non-differential exposure misclassification bias among Marines and Navy personnel, the HRs increased by ≤ 17.1%. For civilian workers, non-differential exposure misclassification bias increased HRs by ≤ 5%.

Table B.3 TCE Exposure at Camp Lejeune and PD Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Bove *et al.* (2014a)	CL civilian employees with < median exposure	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Maximum cumulative exposure level with 10-yr lag[a]					
				≥ Median	4	–	2.51 (0.21-30.76)	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Sex
				Cumulative exposure level (µg/L-mos)[b,c]					
				Low (< 110)	41	–	0.86 (0.47-1.59)	–	
				Medium (110 - < 11,030)	34		0.87 (0.46-1.62)		
				High (≥ 11,030)	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure (< 110 µg/L-mos)			Medium (110 - < 11,030)	34		1.00 (0.63-1.59)		
				High (≥ 11,030)	3		0.33 (0.10-1.09)		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[b,d]					
				Low (< 10,868)	7	–	2.78 (0.87-8.94)	–	
				Medium (10,868 - < 50,563)	10		**3.47 (1.18-10.22)**		
				High (≥ 50,563)	3		2.86 (0.67-12.13)[e]		
	CL civilian employees with low exposure (< 10,868 µg/L-mos)			Medium (10,868 - < 50,563)	10		1.81 (0.69-4.77)		–
				High (≥ 50,563)	3		2.03 (0.52-7.93)[e]		

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; Mo = Month; OR = Odds Ratio; PCE = Perchloroethylene; PD = Parkinson's Disease; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0009, 95% CI: 0.0001-0.0017).

(b) 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).
(c) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).
(d) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).
(e) ATSDR (2018b) reported a positive monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

Table B.4 PCE Exposure at Camp Lejeune and PD Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Bove *et al.* (2014a)	CL civilian employees with < median exposure	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[a]					
				≥ Median	4	–	2.68 (0.22-33.28)	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Sex
				Cumulative exposure level (µg/L-mos)[b]					
				Low (> 0- < 36)	44	–	0.94 (0.51-1.71)	–	
				Medium (36 - < 711)	21		0.54 (0.27-1.05)		
				High (≥ 711)	13		1.22 (0.57-2.61)		
	CL Marines & Navy personnel with low exposure (> 0 - < 36 µg/L-mos)			Medium (36 - < 711)	21		**0.57 (0.34-0.97)**		
				High (≥ 711)	13		1.32 (0.70-2.49)		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[b,c]					
				Low (< 457)	7	–	2.78 (0.87-8.94)	–	
				Medium (457 - < 2,118)	10		**3.47 (1.18-10.22)**		
				High (≥ 2,118)	3		2.86 (0.67-12.13)[d]		
	CL civilian employees with low exposure (< 457 µg/L-mos)			Medium (457 - < 2,118)	10		1.81 (0.69-4.77)		–
				High (≥ 2,118)	3		2.03 (0.52-7.93)[d]		

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; Mo = Month; OR = Odds Ratio; PCE = Perchloroethylene; PD = Parkinson's Disease; TCE = Trichloroethylene; µg/L = Microgram per Liter; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0199, 95% CI: 0.0005-0.0393).
(b) 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).
(c) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).
(d) ATSDR (2018b) reported a positive monotonic exposure-response relationship but the trend was not evaluated for statistical significance.

Table B.5 Benzene Exposure at Camp Lejeune and PD Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Bove *et al.* (2014a)	CL civilian employees with < median exposure	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[a]					
				≥ Median	4	–	2.52 (0.20-31.59)	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Sex
				Cumulative exposure level[b,c]					
				Low	41	–	0.86 (0.47-1.59)	–	
				Medium	34		0.87 (0.46-1.62)		
				High	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure			Medium	34		1.00 (0.63-1.59)		
				High	3		0.33 (0.10-1.09)		

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; Mo = Month; OR = Odds Ratio; PD = Parkinson's Disease; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yr = Year.
– = Not Reported.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0245, 95% CI: 0.0008-0.0971).
(b) Categorized as low exposure (< 50th percentile), medium exposure (≥ 5^{0th} percentile to < 90th percentile), and high exposure (≥ 90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).
(c) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).

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

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Bove *et al.* (2014a)	CL civilian employees with < median exposure	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[a]					
				≥ Median	4	–	2.81 (0.23-34.11)	–	
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Sex
				Cumulative exposure level[b,c]					
				Low	41	–	0.86 (0.47-1.59)	–	
				Medium	34		0.87 (0.46-1.62)		
				High	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure			Medium	34		1.00 (0.63-1.59)		
				High	3		0.33 (0.10-1.09)		

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; Mo = Month; OR = Odds Ratio; PD = Parkinson's Disease; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; VC = Vinyl Chloride; Yr = Year.
– = Not Reported.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0129, 95% CI: 0.0063-0.0253).
(b) 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).
(c) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).

Attachment C

Epidemiology Study Quality Assessment

List of Tables

Table C.1 PD 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										
Bove *et al.* (2014a)	Civilian employees at CL and CP	T	P	B	V	Strengths • Appropriate comparison groups • ≤ 2% loss to follow-up Weaknesses • Most of the cohort was < 65 yrs old by end of follow-up (> 70% CL, > 60% CP)	Strengths • No missing data • Internal analyses considered duration of employment and average exposure Weaknesses • Indirect chemical exposure measurement – based on employment at CL (external analyses) or modeling of groundwater contamination (internal analyses) • External analyses did not consider duration of employment and average exposure	Strengths • Deaths identified from SSA, a commercial tracing service, and NDI; cause of death determined from NDI Plus • No missing data Weaknesses • Assessed mortality only	Strengths • Controlled for: age, and sex in US comparison and sex and occupation in CP and internal comparisons • Considered but did not control for: age in CP and internal comparisons because adjusted *vs.* unadjusted results differed by < 10% • Collected occupation data quarterly during employment Weaknesses • Did not consider or control for: genetic factors or family history of PD, alcohol intake, smoking in any analyses, or other potential occupational exposures in US comparison • Unclear whether occupation was analyzed in a time-varying manner, other covariates only considered at a single time point	Strengths • Employment histories collected separately from outcome data • Appropriate consideration of latency 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 is unknown	
Silver *et al.* (2014)	Microelectronics and business machine facility employees	T	P			Strengths • Appropriate comparison groups Weaknesses • Relatively young cohort (mean age at hire was mid-20s, average follow-up was 25.7 yrs)	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement – based on employment at facility • Missing/incomplete/ conflicting data regarding work dates, facility location, department, and position (particularly for early yrs) • Sparse data during periods of highest chemical use (before 1974)	Strengths • Cases identified from SSA, NDI, and IRS; cause of death determined from NDI and death certificates • No missing data Weaknesses • Assessed mortality only	Strengths • Controlled for: age and sex Weaknesses • Did not consider or control for: genetic factors/family history of PD, heavy alcohol intake, or smoking • Only considered covariates at a single time point • Amount of missing data is unknown	Strengths • Occupational histories collected separately from outcome data • Appropriate consideration of latency (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
ATSDR (2018b)	Marines & Navy personnel and civilian employees at CL and CP	T	P	B	V	Strengths • Appropriate comparison groups Weaknesses • < 25% of CL sample completed health survey • 10% of those who reported an outcome excluded for not completing HIPAA form	Strengths • Some analyses examined cumulative, average, maximum, and duration of exposure • No missing data Weaknesses • Indirect chemical exposure measurement – based on being stationed or employed at CL (external analyses), or modeling of groundwater contamination (internal analyses) • Some external analyses did not examine cumulative, average, maximum, and duration of exposure	Strengths • Self-reported diagnoses confirmed with medical records or death certificates • Assessed PD incidence • No missing data Weaknesses • Initial case identification relied on self-report	Strengths • Controlled for sex in some analyses • Considered but did not control for: age, smoking, alcohol, or other potential occupational exposures/ other chemical exposures (in any analysis), and sex (in some analyses) because adjusted *vs.* unadjusted results differed by < 10% Weaknesses • Information on most covariates was self-reported • Did not consider or control for: genetic factors or family history of PD • Only considered covariates at a single time point • Smoking, alcohol, and other occupational exposures missing for > 5% of participants	Strengths • Up to 40 yrs of follow-up Weaknesses • Did not consider latency period • Exposure period overlaps period of follow-up for PD, 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
Goldman *et al.* (2023)	Marines & Navy personnel at CL					Strengths • Appropriate comparison groups Weaknesses • < 50% of Marines & Navy personnel were included from either base (had to have used VHA or Medicare services)	Strengths • Minimum 3 mos duration of residence • No missing data Weaknesses • Indirect chemical exposure measurement – based on residence at Camp Lejeune • Did not consider duration, intensity, or time-varying nature of exposure	Strengths • Cases identified from VHA and Medicare medical records • Assessed PD incidence • No missing data Weaknesses • Some analyses include "probable" PD	Strengths • Controlled for age, sex, smoking Weaknesses • Smoking status unknown for > 25% • Did not consider or control for genetic factors or family history of PD, alcohol intake, or other possible chemical exposures • Only considered covariates at a single time point	Strengths • Exposure documented prior to outcome • Appropriate consideration of latency (≥ 12 yrs between exposure and outcome) Weaknesses • No major weaknesses
Bove *et al.* (2024a)	Marines & Navy personnel and civilian workers at CL and CP					Strengths • Appropriate study and comparison groups • < 1% 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.*, assignment or employment at base)	Strengths • Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers and NDI) • No missing data Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, race, and (for civilians) occupation (blue *vs.* white collar as a proxy for other potential occupational exposures) • Considered quantitative bias from unmeasured smoking "negative control diseases"	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency (though, 75% of deaths occurred > 10 yrs after water contamination ended)

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
									Weaknesses • Did not control for or consider: family history of PD, heavy alcohol intake, or genetic factors • 5.2% of CL and CP Marines/ Navy subgroup personnel and 14.7% of CP civilians had other/unknown race	
Dorsey *et al.* (2024)	Lawyers in Rochester, NY	T	P			Strengths • High (96.3%) participation in the tower cohort Weaknesses • Only partners included in "exposed" group • Low (63%) participation in the comparison group • Some tower cohort members were deceased, but all comparison group participants were alive • Inappropriate comparison groups	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement – based on being a partner at tower ≥ 1 yr • Did not consider duration, frequency, or intensity of exposure	Strengths • Cases confirmed using medical records and clinical assessments of PD (*e.g.*, Gleb criteria) • Assessed PD incidence • < 5% missing data (missing medical record on one deceased person) Weaknesses • No major weaknesses	Strengths • Controlled for age and sex Weaknesses • Did not consider or control for: race/ ethnicity, smoking, family history of PD, other possible chemical exposures, heavy alcohol intake, or genetic factors • Information on most covariates was self-reported • Amount of missing data unknown	Strengths • Exposure documented separate from outcome (*i.e.*, clinicians masked on exposure status) Weaknesses • Exposure period overlaps period of follow-up for PD, unclear how this was handled in analysis • Insufficient consideration of latency (*i.e.*, ≥ 1 yr as partner at tower)

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Case-Control Studies										
Park *et al.* (2005)	22 US state residents			B		Strengths • Appropriate comparison groups Weaknesses • Number excluded due to incomplete occupational information unknown	Strengths • Considered intensity • No missing data Weaknesses • Indirect benzene exposure measurement – based on JEM • Occupation was self-reported (based on census) • Only considered occupational history at a single time point • Did not consider duration or time-varying nature of exposure	Strengths • Cases identified from death certificates obtained using the National Occupational Mortality Surveillance System Weaknesses • Only assessed mortality	Strengths • Considered: age and sex • No missing data Weaknesses • Did not consider: genetic factors/family history of PD, alcohol consumption, smoking, or other chemical exposures • Assessed covariates at a single time-point	Strengths • Occupation was recorded before outcome Weaknesses • Did not consider latency period

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Goldman *et al.* (2012)	NAS-NRC World War II Veteran Twins Cohort Registry	T	P			Strengths • Appropriate participant selection and comparison groups Weaknesses • Low occupational history completion rate (60-63%) • Small number of exposed participants (10 cases, 3 controls) • Source population (twins with military history) may not represent general population	Strengths • Examined duration and cumulative exposure • No missing data Weaknesses • Indirect chemical exposure measurement – based on self or proxy job/hobby history linked to probability of exposure database • Greater proxy response for cases (46.5%) than controls (18.2%) • Some analysis only used any/ever exposure	Strengths • Cases identified *via* phone survey and VA, HCFA, NDI, and NAS-NRC Registry of Aging Twin Veterans medical records and confirmed by review of in-person evaluation, neurological exam, and medical records by two neurologists • Assessed PD incidence • No missing data Weaknesses • No major weaknesses	Strengths • Study limited to male twins (same age/sex/ genetics) • Primary analyses controlled for: respondent type (*i.e.*, subject or proxy) and smoking • Secondary analyses controlled for certain solvent exposures (toluene, xylene, n-hexane, CCl_4, PCE) • No missing data Weaknesses • Did not consider or control for other solvent exposures or alcohol intake • Only considered covariates at a single time point	Strengths • Average of 38.3 yrs between first exposure and diagnosis • Appropriate consideration of latency in sensitivity analysis (10-yr lag) Weaknesses • Occupational exposure reported after diagnosis • No consideration of exposure preceding outcome or latency in primary analyses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sallmén *et al.* (2023)	Employed Finnish Residents	T	P	B		Strengths • Appropriate participant selection and comparison groups Weaknesses • Approximately half of potential participants were excluded due to missing census or occupational data	Strengths • Considered occupation at multiple time points • Considered duration and intensity of exposure Weaknesses • Indirect chemical exposure measurement – based on job titles reported in censuses linked to FINJEM • Unknown how much census data were missing for included subjects • Did not consider time-varying exposures	Strengths • Cases identified through FSII medical register • Assessed PD incidence • No missing data Weaknesses • Included PD and comparable movement disorders	Strengths • Matched on sex, birth yr, and residency in Finland in 1980-2014 • Adjusted for sex, birth yr, and probability of smoking • Considered other chemical exposures in secondary analyses • No missing data Weaknesses • Smoking probabilities were estimated based on surveys of Finnish residents linked to occupation and sex • Did not consider or control for genetic factors or family history of PD or alcohol intake • Only considered covariates at a single time point (last active census in 1970-1990)	Strengths • Exposure only considered prior to case registration date • Appropriate consideration of latency (≥ 5 yrs between exposure and outcome) Weaknesses • No major weaknesses

Notes:
CCl_4 = Carbon Tetrachloride; CL = Camp Lejeune; CP = Camp Pendleton; FINJEM = Finnish Job Exposure Matrix; FSII = Social Insurance Institution of Finland; HCFA = Health Care Financing Administration; HIPAA = Health Insurance Portability and Accountability Act; IRS = Internal Revenue Service; Mo = Month; NAS-NRC = National Academy of Sciences-National Research Council; NDI = National Death Index; NY = New York; PCE = Perchloroethylene; PD = Parkinson's Disease; SSA = Social Security Administration; TCE = Trichloroethylene; US = United States; VA = Veterans Affairs; VHA = Veterans Health Administration; Yr = Year.

Attachment D

TCE Epidemiology Studies

List of Tables

Table D.1 TCE and PD Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Outcome		
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Type	Ascertainment	Follow-Up Period
Bove *et al.* (2014a)[a]	US	Civilian employees at CL and CP	B	CL: 31-58[b] CP: 34-60[b]	CL: 4,647 CP: 4,690	1973-1985	Average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics and business machine facility employees	B	Mean: 25.7-28.7	34,494	1969-2001	Employment at the facility for ≥ 91 days	Mort	SSA, NDI, and IRS	1969-2009
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 & Navy) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012
Dorsey *et al.* (2024)	US	Lawyers in Rochester, NY	B	Tower cohort: $\bar{x}$ = 69.5 Comparison group: $\bar{x}$ = 64.9	Tower cohort: 79 Comparison group: 75	1968-2001[e]	≥ 1 yr as a partner in a law firm in a tower across the street from a dry-cleaning business that contaminated the surrounding soil with TCE, PCE, and other chemicals[f]	Inc	Self-reported medical history, Gelb Criteria	1968-2023

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; IRS = Internal Revenue Service; Mo = Month; Mort = Mortality; NDI = National Death Index; NY = New York; PD = Parkinson's Disease; SSA = Social Security Administration; TCE = Trichloroethylene; PCE = Perchloroethylene; US = United States; Yr = Year.
$\bar{x}$ = Mean
(a) Bove *et al.* (2014b) evaluated exposures at CL and health outcomes in Marines and Navy personnel using similar methods to those used in Bove *et al.* (2014a). There were < 5 cases of PD observed so they did not evaluate associations in analyses of Marines and Navy personnel.
(b) Median age from start to end of follow-up (Bove *et al.*, 2014a).

(c) Ages and population sizes are reflective of Marines, Navy personnel, 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 (ATSDR, 2013b), some of whom were included in this analysis (ATSDR, 2018b).
(d) Median age range at survey or death (ATSDR, 2018b).
(e) Dorsey *et al*. (2024) did not report when the contamination started, only that the dry cleaner operated from 1950-1994 and that "TCE, PCE, or other chemicals were still found in the exhaust gas from the garage ventilation system until the system was shut down in 2003."
(f) Dorsey *et al*. (2024) reported that other chemicals at the site "included methylene chloride, chloroform, chlorobenzene, 1,4-dichlorobenzene, 1,1,2,2-tetrachloroethane, cis 1,2-dichloroethene, 1,3,5- and 1,2,4–trimethylbenzene, isopropylbenzene, n-propylbenzene, sec-, and tert-butylbenzene, acetone, ethylbenzene, isopropylbenzene, naphthalene, toluene, p-isopropyltoluene, m-o- and p-xylene, and Stoddard solvent." They also stated that "because the groundwater at the site was not used for drinking, it was not extensively sampled or analyzed" (Dorsey *et al*., 2014), so chemical concentrations are unknown.

Table D.2 TCE and PD Cohort Study Results

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Mortality								
Bove *et al.* (2014a)	CL civilian employees with < median exposure	HR	**CL Civilian Employees**					
			Maximum cumulative exposure level with 10-yr lag[b]					
			≥ Median	4	–	2.51 (0.21-30.76)	–	Age, sex, race, blue- or white-collar occupation, and education
Silver *et al.* (2014)	US general population	SMR	**Total Cohort (Not Chemical Specific) (10-Yr Lag)**					
			Males					
			Hourly	21	–	0.87 (0.54-1.34)	–	Age, sex, race, and calendar time
			Salaried	19		1.21 (0.73-1.89)		
			Females					
			Hourly	3	–	0.73 (0.15-2.14)	–	Age, sex, race, and calendar time
			Salaried	0		0.00 (0.00-21.8)		

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Incidence								
ATSDR (2018b)	CP Marines & Navy personnel	OR	**CL Marines & Navy Personnel**					
			Cumulative exposure level (µg/L-mos)[c,d]					
			Low (< 110)	41	–	0.86 (0.47-1.59)	–	Sex
			Medium (110 - < 11,030)	34		0.87 (0.46-1.62)		
			High (≥ 11,030)	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure (< 110 µg/L-mos)		Medium (110 - < 11,030)	34		1.00 (0.63-1.59)		
			High (≥ 11,030)	3		0.33 (0.10-1.09)		
	CP civilian employees		**CL Civilian Employees**					
			Cumulative exposure level (µg/L-mos)[c,e]					
			Low (< 10,868)	7	–	2.78 (0.87-8.94)	–	Sex
			Medium (10,868 - < 50,563)	10		**3.47 (1.18-10.22)**		
			High (≥ 50,563)	3		2.86 (0.67-12.13)[f]		
	CL civilian employees with low exposure (< 10,868 µg/L-mos)		Medium (10,868 - < 50,563)	10		1.81 (0.69-4.77)		–
			High (≥ 50,563)	3		2.03 (0.52-7.93)[f]		
Dorsey *et al.* (2024)	General population	–[g]	Tower cohort	4	–[h]	**0.01**	–	Age and sex
	Attorneys who worked ≥ 1 yr at other locations in Rochester, NY			4		0.21		Age at time of assessment or at time of death

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mo = Month; NY = New York; OR = Odds Ratio; PCE = Perchloroethylene; PD = Parkinson's Disease; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; µg/L = Microgram per Liter; US = United States; VC = Vinyl Chloride; Yr = Year.
– = Not Reported.
Bold text indicates statistical significance.
(a) Expected cases for SMR analyses and exposed non-cases for other analyses.
(b) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0009, 95% CI: 0.0001-0.0017).

(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, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).
(e) The correlation between TCE and PCE was ~1 (ATSDR, 2018b).
(f) ATSDR (2018b) reported a positive monotonic exposure-response relationship, but the trend was not evaluated for statistical significance.
(g) Dorsey *et al*. (2024) reported the *p* value from a binomial test or a Fisher's exact test comparing the prevalence of PD in the tower cohort to the prevalence in the general population or the lawyer comparison group, respectively.
(h) Dorsey *et al*. (2024) reported the expected prevalence of PD in the general population based on age and sex was 1.7%, compared to the observed 5.1%. There was one PD case reported in the lawyer comparison group.

Table D.3 TCE and PD Case-Control Study Characteristics

Study	Location	Study Period[a]	Study Population							Exposure Ascertainment
			Sex	Age (Yrs)	Cases			Controls		
					N	Type	Source	N	Source	
Goldman *et al.* (2012)	US	1993-1995	M	–	99	Inc	VA, HCFA, and NDI, and NAS-NRC Registry of Aging Twin Veterans	99	Twin brothers of the cases	Estimated based on self-reported lifetime job and hobby histories
Sallmén *et al.* (2023) [Nielsen *et al.*, 2021]	Finland	1980-2014	B	45-84	17,187	Inc	FSII-medication reimbursement register	35,738	The Population Information System	Occupation reported in each census (1970-2008) linked to FINJEM (1950-2009)

Notes:

B = Both Males and Females; FINJEM = Finnish Job Exposure Matrix; FSII = Social Insurance Institution of Finland; HCFA = Health Care Financing Administration; Inc = Incidence; M = Males; NAS-NRC = National Academy of Sciences-National Research Council; NDI = National Death Index; PD = Parkinson's Disease; TCE = Trichloroethylene; US = United States; VA = Veterans Affairs; 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) Dates of case ascertainment.

Table D.4 TCE and PD Case-Control Study Results

Study	Statistical Analysis						
	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Incidence							
Goldman *et al.* (2012)	OR	Any TCE exposure	10	3	**6.1 (1.2-33)**	–	Respondent type and smoking
		TCE exposure duration, by 1-tertile difference	10	3	**3.2 (1.1-10)**		
		TCE CEI, by 1-tertile difference	10	3	**5.2 (1.03-26)**		
Sallmén *et al.* (2023)[a]	IRR	**Cumulative TCE Exposure (ppm-yrs)**					
		0	15,243	–	Ref	–	Birth yr, sex, SES, and probability of smoking
		> 0-4.9	617		0.95 (0.86-1.05)		
		5-14.9	416		0.97 (0.87-1.10)		
		15-225	338		1.03 (0.90-1.18)		

Notes:
CEI = Cumulative Exposure Index; CI = Confidence Interval; IRR = Incidence Rate Ratio; OR = Odds Ratio; PD = Parkinson's Disease; ppm = Parts per Million; Ref. = Reference; SES = Socioeconomic Status; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bold text indicates statistical significance.
(a) Sallmén *et al.* (2023) also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to a chemical-specific method) and probabilistic bias analyses (PBA) that accounted for exposure measurement error. The results from the PBA analyses were shifted to the null. PBA analyses were not run for TCE-specific exposures.

Attachment E

TCE Animal Carcinogenicity Studies

List of Tables

Table E.1 TCE and PD Subchronic Inhalation Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period (Wks)	Treatment Groups (n and Sex)	Dose (ppm)	PD-Associated Outcomes								
						A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Adamson *et al.* (2023)	Lewis rat	8	8	4-8 M	0	No	–	–	No	–	No	–	–	No
					50	**	–	–	***	–	***	–	–	*
				4-8 F	0	No	–	–	No	–	No	–	–	No
					50	**	–	–	***	–	***	–	–	*
	C57BL/6J mouse	12	12	8-14 M	0	–	–	–	No	–	No	–	–	No
					100	–	–	–	*	–	**	–	–	*
				8-14 F	0	–	–	–	No	–	No	–	–	No
					100	–	–	–	*	–	**	–	–	*

Notes:
A = Accumulation of α-Synuclein in SNpc; D = Decreased Dopamine Levels in SNpc; Dm = Decreased Dopamine Metabolite Levels in SNpc; Dn = Loss of Dopamine Neurons in SNpc; Dr = Decreased Dopamine Receptor Levels in SNpc; Dtrm = Decreased Dopamine Neuron Terminals; Dtrp = Decreased Dopamine Transporter Levels in SNpc; F = Females; M = Males; Mi = Decreased Mitochondrial Function in SNpc; Mo = Decreased Motor Function; PD = Parkinson's Disease; ppm = Parts per Million; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene; Wk = Week.
– = Not Examined; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.

Table E.2 TCE and PD Subchronic Oral Study Results

Study	Strain/ Species	Exposure Duration (Wks)	Observation Period (Wks)	Treatment Groups (n and Sex)	Dose (mg/kg-d)	PD-Associated Outcomes								
						A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Gash *et al.* (2008)[a-d]	Fischer 344 rat	6	6	3-17 M	0	No	No	No	No	–	–	–	No	–
					1,000	NR	*	**	**	–	–	–	**	–
Liu *et al.* (2010)[a,b,e-g]	Fischer 344 rat	6	2 or 6	6-9 M	0	No	No	No	No	–	–	–	No	No
					200	–	–	–	No	–	–	–	–	–
					500	–	–	–	*	–	–	–	–	–
					1,000	NR	No	**	**	–	–	–	*	*
Liu *et al.* (2018)[b,h]	C57BL/6 mouse	13	13	8-10 M	0	–	–	–	No	No	–	–	–	–
					400	–	–	–	*	Yes	–	–	–	–
		35	35		0	No	No	No	No	No	–	–	No	No
					400	**	**	**	**	No	–	–	*	**
De Miranda *et al.* (2021)[b,i]	Lewis rat	1-6	1-6	7 M	0	No	–	–	No	–	No	–	–	No
				10 M	200	**	–	–	****	–	**	–	–	*
				10 F	200	–	–	–	–	–	****	–	–	–
Ilieva *et al.* (2022)	Lewis rat	6	6	5 F	0	–	–	–	–	–	–	–	–	–
					200	–	–	–	–	–	–	–	–	–
Ilieva *et al.* (2024)[b,j]	Lewis rat	3	3	5 F	0	–	–	–	NS	–	–	–	–	–
					200	–	–	–	NS	–	–	–	–	–
		6	6		0	–	–	–	NS	–	–	–	NS	–
					200	–	–	–	****	–	–	–	***	–
					200 + MLi2	–	–	–	***	–	–	–	****	–
Srivastava *et al.* (2024)[k]	Wistar rat	8	4-8	6 M	0	–	–	–	NS	–	–	–	–	NS
					1,000	–	–	–	NR	–	–	–	–	****
					1,000 + Levodopa + Carbidopa	–	–	–	NR	–	–	–	–	****
					1,000 + ALP (pure)	–	–	–	NR	–	–	–	–	****
					1,000 + ALP-SENF (50 mg/kg)	–	–	–	NR	–	–	–	–	****
					1,000 + ALP-SENF (100 mg/kg)	–	–	–	NR	–	–	–	–	****

Notes:
A = Accumulation of α-Synuclein in SNpc; D = Decreased Dopamine Levels in SNpc; Dm = Decreased Dopamine Metabolite Levels in SNpc; Dn = Loss of Dopamine Neurons in SNpc; Dr = Decreased Dopamine Receptor Levels in SNpc; Dtrm = Decreased Dopamine Neuron Terminals; Dtrp = Decreased Dopamine Transporter Levels in SNpc; F = Female; M = Male; mg/kg-d = Milligram per Kilogram per Day; Mi = Decreased Mitochondrial Function in SNpc; Mo = Decreased Motor Function; NR = Statistical Significance Was Not Reported; PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene; Wk = Week.
– = Not Examined; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.
(a) The statistical significance of α-synuclein accumulation was not assessed.
(b) The magnitude of loss of dopaminergic neurons was less than that required to produce clinical signs of PD in humans (50-70%) (Dauer and Przedborski, 2003; Lock *et al*., 2013; Keane *et al*., 2019; Hur and Lee, 2021).
(c) Mitochondrial function (*i.e*., respiratory activity of complex I) was examined in 3 male rats/treatment. Dopaminergic neuron immunohistochemistry was examined in 17 male rats/treatment.
(d) PD-associated pathological outcomes were also examined in the striatum (not reported here). In the striatum, there was statistically significant decreased dopamine metabolism, but a statistically significant increase in mitochondrial complex I activity (noted to be a potential compensatory response), and no effect on dopamine levels. No pathological effects were consistently observed in both brain regions.
(e) Mitochondrial function (*i.e*., respiratory activity of complex I) was examined in 9 male rats per treatment. Dopaminergic neuron immunohistochemistry was examined in 6 male rats/treatment. Motor function was assessed by the rotarod test and spontaneous locomotor activity test in 8 male rats/treatment.
(f) There was no decrease in dopamine levels in striatum and no loss of neurons in extranigral brain regions; these findings are inconsistent with PD.
(g) Inconsistent effects were observed in motor function tests, specifically, TCE exposure significantly reduced motor performance and coordination as measured by rotarod test (at 5 and 6 wks of TCE treatment, but not at ≤ 4 wks of treatment), but had no effect on spontaneous locomotor activity.
(h) Mitochondrial function (*i.e*., respiratory activity of complex I) was examined in 10 male mice per treatment. Dopaminergic neuron immunohistochemistry was examined in 8 male mice per treatment. Motor function was assessed by the rotarod test and open field test in 8 male mice per treatment.
(i) Seven male rats per treatment group were exposed to TCE for 6 wks and examined for α-synuclein accumulation. Seven male rats per treatment were exposed to TCE for 8 wks and examined for dopaminergic neuron immunohistochemistry. Eight male rats per treatment were exposed to TCE for 6 wks and prior to motor function assessment by open field test.
(j) Ilieva *et al*. (2024) treated rats with 200 mg/kg-d TCE with MLi2 but reported statistical significance of outcomes relative to the TCE exposure group only, not relative to controls.
(k) Srivastava *et al*. (2024) treated rats with 1,000 mg/kg-d TCE and PD therapeutic compounds (Levodopa + Carbidopa) or an antioxidant compound (ALP-SENF), but reported statistical significance of outcomes relative to the TCE exposure group only, not relative to controls.

Table E.3 TCE and PD Subchronic Intraperitoneal Injection Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period (Wks)	Treatment Groups (n and Sex)	Dose (mg/kg-d)	PD-Associated Outcomes								
						A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Keane *et al.* (2019)[a,b]	C57BL/6 mouse	8	42	3-5 M and F	0	–	–	–	No	–	–	–	–	No
					1,000	–	–	–	***	–	–	–	–	No
	C57BL/6 mouse overexpressing A30P mutant human α-synuclein				0	–	–	–	No	–	–	–	–	No
					1,000	–	–	–	***	–	–	–	–	No

Notes:

A = Accumulation of α-Synuclein in SNpc; D = Decreased Dopamine Levels in SNpc; Dm = Decreased Dopamine Metabolite Levels in SNpc; Dn = Loss of Dopamine Neurons in SNpc; Dr = Decreased Dopamine Receptor Levels in SNpc; Dtrm = Decreased Dopamine Neuron Terminals; Dtrp = Decreased Dopamine Transporter Levels in SNpc; F = Females; i.p. = Intraperitoneal; M = Males; mg/kg-d = Milligram per Kilogram per Day; Mi = Decreased Mitochondrial Function in SNpc; Mo = Decreased Motor Function; PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene; Wk = Week.

– = Not Examined; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.

(a) The authors concluded that exposure to TCE "can cause [dopamine] neuronal cell death in the SNpc in vivo, suggesting TCE exposure as a possible contributory factor in development of PD." However, the authors acknowledged that there were no significant effects on motor function: "TCE or TaClo did not appear to lead to acceleration of motor or cognitive deficits in either wild type or A30P mutant mice, potentially because of the modest reductions of [dopamine] neuronal number in the SNpc." The authors further concluded, "It is possible that the levels of [dopamine] cell death in the SNpc of treated animals are insufficient to cause motor dysfunction since over 70-80% SNpc cell death is required before behavioural deficits are seen."

(b) It should be noted that intraperitoneal injection exposure is not relevant to environmental or occupational exposures in humans.

Table E.4 TCE and PD Subacute Oral Study Results

Study	Strain/ Species	Exposure Duration (Wks)	Observation Period (Wks)	Treatment Groups (n and Sex)	Dose (mg/kg-d)	PD-Associated Outcomes								
						A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Sauerbeck *et al.* (2012)[a,b]	Fischer 344 rat	1	5-6 weeks	33 M	0	–	–	–	No	No	–	No	–	No
					1,000	–	–	–	No	No	–	No	–	No
		2			0	–	–	–	No	No	–	No	No	No
					1,000	–	–	–	No	No	–	No	No	No

Notes:
A = Accumulation of α-Synuclein in SNpc; D = Decreased Dopamine Levels in SNpc; Dm = Decreased Dopamine Metabolite Levels in SNpc; Dn = Loss of Dopamine Neurons in SNpc; Dr = Decreased Dopamine Receptor Levels in SNpc; Dtrm = Decreased Dopamine Neuron Terminals; Dtrp = Decreased Dopamine Transporter Levels in SNpc; M = Males; mg/kg-d = Milligram per Kilogram per Day; Mi = Decreased Mitochondrial Function in SNpc; Mo = Decreased Motor Function; PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene; Wk = Week.
– = Not Examined; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.
(a) TCE exposure did not affect mitochondrial complex I activity in the SNpc, whereas complex I activity was reduced by approximately 75% in the striatum ($p < 0.05$).
(b) The authors concluded that under these experimental conditions, TCE exposure alone (without induction of simulated traumatic brain injury) was "individually insufficient to produce motor impairment or a loss of TH-positive neurons [*i.e.*, dopamine neurons] – hallmarks of human PD."

Table E.5 TCE and PD Subacute Intraperitoneal Injection Study Results

Study	Strain/ Species	Exposure Duration (Wks)	Observation Period (Wks)	Treatment Groups (n and Sex)	Dose (mg/kg-d)	PD-Associated Outcomes								
						A	D	Dm	Dn	Dr	Dtrm	Dtrp	Mi	Mo
Guehl *et al.* (1999)[a]	OF1 mouse	4	5	10 M	0	–	–	–	No	–	–	–	–	No
					400	–	–	–	***	–	–	–	–	No
Otsuki *et al.* (2016)[b]	C57BL/6 background $SOD^{-/-}$ mouse	4	4	5-12 M	0	–	No	No	No	–	–	–	–	No
					400	–	No	No	No	–	–	–	–	No

Notes:
A = Accumulation of α-Synuclein in SNpc; D = Decreased Dopamine Levels in SNpc; Dm = Decreased Dopamine Metabolite Levels in SNpc; Dn = Loss of Dopamine Neurons in SNpc; Dr = Decreased Dopamine Receptor Levels in SNpc; Dtrm = Decreased Dopamine Neuron Terminals; Dtrp = Decreased Dopamine Transporter Levels in SNpc; M = Males; Mi = Decreased Mitochondrial Function in SNpc; mg/kg-d = Milligram per Kilogram per Day; Mo = Decreased Motor Function; PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene; Wk = Week.
– = Not Examined; *** = $p < 0.001$.
(a) The authors stated, "[T]he results afforded by this study underline the possibility that environmental trichloroethylene pollution contributes to the genesis of Parkinson's disease." However, the authors acknowledged that "[t]he trichloroethylene-treated mice presented no parkinsonian motor abnormalities."
(b) The authors noted that the results of the current study were inconsistent with the results of the subacute oral study by Guehl *et al.* (1999) and the subchronic oral study by Liu *et al.* (2010) potentially due to difference in experimental conditions: "The inconsistent results regarding cell death and monoamine metabolites among the studies might be partly attributed to the difference in the amount of TCE used, species, or the strain of rodents used" (Otsuki *et al.*, 2016).

Table E.6 TCE and PD Subchronic and Subacute Study Quality Overview

Parameter	Summary
Reporting	All studies reported sufficient information on the species, test article name, experimental design, exposure conditions, and outcome evaluation methods.
Allocation	None of the studies stated that animals were randomly allocated to dose groups, except for Keane *et al.* (2019), De Miranda *et al.* (2021), Adamson *et al.* (2023), and Ilieva *et al.* (2024).
Bias	There was no indication that there were differences across treatment groups that could bias results in any study.
Sample	Three subchronic oral studies (Ilieva *et al.*, 2022, 2024; Srivastava *et al.*, 2024), one subacute oral bioassay (Sauerbeck *et al.*, 2012), and two subacute intraperitoneal injection studies (Guehl *et al.*, 1999; Otsuki *et al.*, 2016) had adequate sample sizes. In all remaining studies, one or more exposure groups had a sample size that was too small.
Chemical Administration and Characterization	None of the studies independently verified chemical purity or took steps to ensure reported exposure levels were accurate.
Exposure Conditions	Except for Liu *et al.* (2010), only one high dose was evaluated per species, precluding evaluation of a dose-response effect for any examined parameters. In addition, the single high doses tested in all the oral and intraperitoneal exposure studies ranged from 200 to 1,000 mg/kg-d and have unclear relevance to humans. Finally, the subchronic and subacute exposure durations are too short to assess PD, a chronic, progressive disease.
Outcome Assessment	Ilieva *et al.* (2022) did not evaluate any pathological outcomes in the SNpc. Only five studies evaluated motor function in conjunction with effects on at least one PD-associated health outcomes (*e.g.*, dopaminergic neuron loss) (Liu *et al.*, 2010, 2018; De Miranda *et al.*, 2021; Adamson *et al.*, 2023; Srivastava *et al.*, 2024). However, Srivastava *et al.* (2024) did not report the magnitude or statistical significance of dopaminergic neuron loss, nor was the evaluation conducted in the SNpc, specifically. None of the studies evaluated dopamine content in SNpc, except Gash *et al.* (2008), Otsuki *et al.* (2016), and Liu *et al.* (2018). All studies observed animals over a short duration of < 52 weeks, which is not appropriate for Parkinson's Disease given it is a chronic condition.

Notes:
mg/kg-d = Milligram per Kilogram per Day; PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene.

Table E.7 TCE and PD Subchronic and Subacute Toxicity Study Quality Assessment

Study	Strengths	Weaknesses	Human Relevance
Subchronic – Inhalation			
Adamson *et al.* (2023)	Reporting Allocation Bias	**Sample:** Small sample size (all rats and TCE-exposed mice) **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested per species; uncertain relevance of doses to humans; observation period too short	**Limited:** Low study quality
Subchronic – Oral			
Gash *et al.* (2008)	Reporting Bias	**Sample:** Small sample size (for mitochondrial function) **Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested; inappropriate dose selection; motor function was not assessed; observation period too short	**Limited:** Low study quality
Liu *et al.* (2010)	Reporting Bias	**Sample:** Small sample size **Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested (except dopaminergic neuron number study); inappropriate dose selection; observation period too short	**Limited:** Low study quality
Liu *et al.* (2018)	Reporting Bias	**Sample:** Small sample size (all studies except mitochondrial function) **Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality

Study	Strengths	Weaknesses	Human Relevance
De Miranda *et al.* (2021)	Reporting Allocation Bias	**Sample:** Small sample size (control group) **Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality
Ilieva *et al.* (2022)	Reporting Bias Sample	**Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Only one high dose tested; exposure duration too short to assess PD **Outcome Assessment:** Motor function and SNpc pathology were not assessed; observation period too short	**Limited:** Low study quality
Ilieva *et al.* (2024)	Reporting Allocation Bias Sample	**Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Only one high dose tested; exposure duration too short to assess PD **Outcome Assessment:** Motor function was not assessed; observation period too short	**Limited:** Low study quality
Srivastava *et al.* (2024)	Reporting Bias Sample	**Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Only one high dose tested; exposure duration too short to assess PD **Outcome Assessment:** Magnitude and statistical significance of dopaminergic neuron loss were not assessed; observation period too short	**Limited:** Low study quality
Subchronic – Intraperitoneal Injection			
Keane *et al.* (2019)	Reporting Allocation Bias	**Sample:** Small sample size **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Exposure route inappropriate; only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality

Study	Strengths	Weaknesses	Human Relevance
Subacute – Oral			
Sauerbeck *et al.* (2012)	Reporting Bias Attrition Sample	**Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality
Subacute – Intraperitoneal Injection			
Guehl *et al.* (1999)	Reporting Bias Attrition Sample	**Allocation:** Did not specify whether allocation to exposure groups was random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Exposure route inappropriate; only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality
Otsuki *et al.* (2016)	Reporting Bias Attrition Sample	**Allocation:** Did not specify whether random **Chemical Administration and Characterization:** Did not verify purity or exposure levels **Exposure Conditions:** Exposure duration inadequate **Outcome Assessment:** Exposure route inappropriate; only one dose tested; inappropriate dose selection; observation period too short	**Limited:** Low study quality

Notes:
PD = Parkinson's Disease; SNpc = Substantia Nigra Pars Compacta; TCE = Trichloroethylene.

Attachment F

PCE Epidemiology Studies

List of Tables

Table F.1 PCE and PD Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Outcome		
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Type	Ascertainment	Follow-Up Period
Bove *et al.* (2014a)[a]	US	Civilian employees at CL and CP	B	CL: 31-58[b] CP: 34-60[b]	CL: 4,647 CP: 4,690	1973-1985	Average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics and business machine facility employees	B	Mean: 25.7-28.7	34,494	1969-2001	Employment at the facility for ≥ 91 days	Mort	SSA, NDI, and IRS	1969-2009
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 & Navy) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012
Dorsey *et al.* (2024)	US	Lawyers in Rochester, NY	B	Tower cohort: $\bar{x}$ = 69.5 Comparison group: $\bar{x}$ = 64.9	Tower cohort: 79 Comparison group: 75	1968-2001[e]	≥ 1 yr as a partner in a law firm in a tower across the street from a dry-cleaning business that contaminated the surrounding soil with TCE, PCE, and other chemicals[f]	Inc	Self-reported medical history, Gelb Criteria	1968-2023

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; IRS = Internal Revenue Service; Mo = Month; Mort = Mortality; NDI = National Death Index; NY = New York; PCE = Perchloroethylene; PD = Parkinson's Disease; SSA = Social Security Administration; TCE = Trichloroethylene; US = United States; VHA = Veterans Health Administration; Yr = Year.
$\bar{x}$ = Mean.
(a) Bove *et al.* (2014b) evaluated exposures at CL and health outcomes in Marines and Navy personnel using similar methods to those used in Bove *et al.* (2014a). There were < 5 cases of PD observed so they did not evaluate associations in analyses of Marines and Navy personnel.

(b) Median age from start to end of follow-up (Bove *et al*., 2014a).
(c) Ages and population sizes are reflective of Marines, Navy personnel, 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 (ATSDR, 2013b), some of whom were included in this analysis (ATSDR, 2018b).
(d) Median age range at survey or death (ATSDR, 2018b).
(e) Dorsey *et al*. (2024) did not report when the contamination started, only that the dry cleaner operated from 1950-1994 and that "TCE, PCE, or other chemicals were still found in the exhaust gas from the garage ventilation system until the system was shut down in 2003."
(f) Dorsey *et al*. (2024) reported that other chemicals at the site "included methylene chloride, chloroform, chlorobenzene, 1,4-dichlorobenzene, 1,1,2,2-tetrachloroethane, cis 1,2-dichloroethene, 1,3,5- and 1,2,4–trimethylbenzene, isopropylbenzene, n-propylbenzene, sec-, and tert-butylbenzene, acetone, ethylbenzene, isopropylbenzene, naphthalene, toluene, p-isopropyltoluene, m-o-and p-xylene, and Stoddard solvent." They also stated that "because the groundwater at the site was not used for drinking, it was not extensively sampled or analyzed," (Dorsey *et al*., 2014) so chemical concentrations are unknown.

Table F.2 PCE and PD Cohort Study Results

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Mortality								
Bove *et al.* (2014a)	CL civilian employees with < median exposure	HR	**CL Civilian Employees**					
			Maximum cumulative exposure level with 10-yr lag[b]					
			≥ Median	4	–	2.68 (0.22-33.28)	–	Age, sex, race, blue- or white-collar occupation, and education
Silver *et al.* (2014)	US general population	SMR	**Total Cohort (Not Chemical Specific) (10-Yr Lag)**					
			Males					
			Hourly	21	–	0.87 (0.54-1.34)	–	Age, sex, race, and calendar time
			Salaried	19		1.21 (0.73-1.89)		
			Females					
			Hourly	3	–	0.73 (0.15-2.14)	–	Age, sex, race, and calendar time
			Salaried	0		0.00 (0.00-21.8)		
Incidence								
ATSDR (2018b)	CP Marines & Navy personnel	OR	**CL Marines & Navy Personnel**					
			Cumulative exposure level (µg/L-mos)[c]					
			Low (> 0 - < 36)	44	–	0.94 (0.51-1.71)	–	Sex
			Medium (36 - < 711)	21		0.54 (0.27-1.05)		
			High (≥ 711)	13		1.22 (0.57-2.61)		
	CL Marines & Navy personnel with low exposure (> 0 - < 36 µg/L-mos)		Medium (36 - < 711)	21		**0.57 (0.34-0.97)**		
			High (≥ 711)	13		1.32 (0.70-2.49)		
	CP civilian employees		**CL Civilian Employees**					
			Cumulative exposure level (µg/L-mos)[c,d]					
			Low (< 457)	7	–	2.78 (0.87-8.94)	–	Sex
			Medium (457 - < 2,118)	10		**3.47 (1.18-10.22)**		
			High (≥ 2,118)	3		2.86 (0.67-12.13)[e]		
	CL civilian employees with low exposure (< 457 µg/L-mos)		Medium (457 - < 2,118)	10		1.81 (0.69-4.77)		–
			High (≥ 2,118)	3		2.03 (0.52-7.93)[e]		

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Dorsey *et al.* (2024)	General population	–[f]	Tower cohort	4	–[g]	**0.01**	–	Age and sex
	Attorneys who worked ≥ 1 yr at other locations in Rochester, NY			4		0.21		Age at time of assessment or at time of death

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mo = Month; OR = Odds Ratio; PCE = Perchloroethylene; PD = Parkinson's Disease; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; µg/L = Microgram per Liter; US = United States; Yr = Year.
– = Not Reported.
Bold text indicates statistical significance.
(a) Expected cases for SMR analyses and exposed non-cases for other analyses.
(b) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0199, 95% CI: 0.0005-0.0393).
(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 (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles, because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(d) The correlation between TCE and PCE was ~1 (ATSDR, 2018b).
(e) ATSDR (2018b) reported a positive monotonic exposure-response relationship, but the trend was not evaluated for statistical significance.
(f) Dorsey *et al.* (2024) reported the *p* value from a binomial test or a Fisher's exact test comparing the prevalence of PD in the tower cohort to the prevalence in the general population or the lawyer comparison group, respectively.
(g) Dorsey *et al.* (2024) reported the expected prevalence of PD in the general population based on age and sex was 1.7%, compared to the observed 5.1%. There was one PD case reported in the lawyer comparison group.

Table F.3 PCE and PD Case-Control Study Characteristics

Study	Location	Study Period[a]	Study Population							Exposure Ascertainment
			Sex	Age (Yrs)	Cases			Controls		
					N	Type	Source	N	Source	
Goldman *et al.* (2012)	US	1993-1995	M	–	99	Inc	VA, HCFA, and NDI, and NAS-NRC Registry of Aging Twin Veterans	99	Twin brothers of the cases	Estimated based on self-reported lifetime job and hobby histories
Sallmén *et al.* (2023) [Nielsen *et al.*, 2021]	Finland	1980-2014	B	45-84	17,187	Inc	FSII-medication reimbursement register	35,738	The Population Information System	Occupation reported in each census (1970-2008) linked to FINJEM (1950-2009)

Notes:
B = Both Males and Females; FINJEM = Finnish Job Exposure Matrix; FSII = Social Insurance Institution of Finland; HCFA = Health Care Financing Administration; Inc = Incidence; M = Males; NAS-NRC = National Academy of Sciences-National Research Council; NDI = National Death Index; PCE = Perchloroethylene; PD = Parkinson's Disease; US = United States; VA = Veterans Affairs; 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) Dates of case ascertainment.

Table F.4 PCE and PD Case-Control Study Results

Study	Statistical Analysis						
	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariates Adjusted For
Incidence							
Goldman *et al.* (2012)	OR	Any PCE exposure	5	1	10.5 (0.97-113)	–	Respondent type and smoking
		PCE exposure duration, by 1-tertile difference	5	1	3.4 (0.9-12)		
		PCE CEI, by 1-tertile difference	5	1	9.3 (0.8-100)		
Sallmén *et al.* (2023)[a]	IRR	**Cumulative PCE Exposure (ppm-yrs)**					
		0	16,845	–	Ref	–	Birth yr, sex, SES, and probability of smoking
		> 0-4.9	219		0.96 (0.82-1.13)		
		5-145	123		1.03 (0.83-1.28)		

Notes:
CEI = Cumulative Exposure Index; CI = Confidence Interval; IRR = Incidence Rate Ratio; OR = Odds Ratio; PCE = Perchloroethylene; PD = Parkinson's Disease; ppm = Parts per Million; Ref = Reference; SES = Socioeconomic Status, Yr = Year.
– = Not Reported.
(a) Sallmén *et al.* (2023) also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to chemical-specific method) and probabilistic bias analyses (PBA) that accounted for exposure measurement error. The results from the PBA analyses were shifted to the null. PBA analyses were not run for PCE-specific exposures.

Attachment G

Benzene Epidemiology Studies

List of Tables

Table G.1 Benzene and PD Cohort Study Characteristics

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

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; Mo = Month; Mort = Mortality; NDI = National Death Index; PD = Parkinson's Disease; SSA = Social Security Administration; TCE = Trichloroethylene; US = United States; Yr = Year.
(a) Bove *et al.* (2014b) evaluated exposures at CL and health outcomes in Marines and Navy personnel using similar methods to those used in Bove *et al.* (2014a). There were < 5 cases of PD observed so they did not evaluate associations in analyses of Marines and Navy personnel.
(b) Median age from start to end of follow-up (Bove *et al.*, 2014a).
(c) Ages and population sizes are reflective of Marines, Navy personnel, 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 (ATSDR, 2013b), some of whom were included in this analysis (ATSDR, 2018b).
(d) Median age range at survey or death (ATSDR, 2018b).

Table G.2 Benzene and PD Cohort Study Results

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{Trend}	Covariates Adjusted For
Mortality								
Bove *et al.* (2014a)	CL civilian employees with < median exposure	HR	**CL Civilian Employees**					
			Maximum cumulative exposure level with 10-yr lag[a]					
			≥ Median	4	–	2.52 (0.20-31.59)	–	Age, sex, race, blue- or white-collar occupation, and education
Incidence								
ATSDR (2018b)	CP Marines & Navy personnel	OR	**CL Marines & Navy Personnel**					
			Cumulative exposure level[b]					
			Low	41	–	0.86 (0.47-1.59)	–	Sex
			Medium	34		0.87 (0.46-1.62)		
			High	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure		Medium	34		1.00 (0.63-1.59)		
			High	3		0.33 (0.10-1.09)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mo = Month; OR = Odds Ratio; PD = Parkinson's Disease; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compounds; µg/L = Microgram per Liter; US = United States; Yr = Year.
– = Not Reported.
Bold text indicates statistical significance.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient = 0.0245, 95% CI: 0.0008-0.0971).
(b) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses. Categorized levels 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).

Table G.3 Benzene and PD Case-Control Study Characteristics

Study	Location	Study Period[a]	Study Population							Exposure Ascertainment
			Sex	Age (Yrs)	Cases			Controls		
					N	Type	Source	N	Source	
Park *et al.* (2005)	US	1992-1998	B	–	33,678	Mort	NOMSS	2,501,541	NOMSS	JEM
Sallmén *et al.* (2023) [Nielsen *et al.*, 2021]	Finland	1980-2014	B	45-84	17,187	Inc	FSII-medication reimbursement register	35,738	The Population Information System	Occupation reported in each census (1970-2008) linked to FINJEM (1950-2009)

Notes:
B = Both Males and Females; FINJEM = Finnish Job Exposure Matrix; FSII = Social Insurance Institution of Finland; Inc = Incidence; JEM = Job Exposure Matrix; Mort = Mortality; NOMSS = National Occupational Mortality Surveillance System; 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) Dates of case ascertainment.

Table G.4 Benzene and PD Case-Control Study Results

Study	Statistical Analysis						
	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariates Adjusted For
Incidence							
Park *et al.* (2005)	OR	Any benzene exposure	6,999	603,519	1.05 (0.98-1.12)	–	Age, sex, race, SES, and region
Sallmén *et al.* (2023)[a]	IRR	**Cumulative Benzene Exposure (ppm-yrs)**					
		0	15,762	–	Ref		Birth yr, sex, SES, and probability of smoking
		> 0-1.9	1,094		1.02 (0.95-1.11)		
		2-90	331		1.03 (0.90-1.18)		

Notes:
CI = Confidence Interval; IRR = Incidence Rate Ratio; OR = Odds Ratio; PD = Parkinson's Disease; ppm = Parts per Million; Ref = Reference; SES = Socioeconomic Status; Yr = Year.
– = Not Reported.
(a) Sallmén *et al.* (2023) also evaluated the association between any chlorinated hydrocarbon exposure and PD using conventional models (similar to chemical-specific method) and probabilistic bias analyses (PBA) that accounted for exposure measurement error. The results from the PBA analyses were shifted to the null. PBA analyses were not run for benzene-specific exposures.

Attachment H

Vinyl Chloride Epidemiology Studies

List of Tables

Table H.1 Vinyl Chloride and PD Cohort Study Characteristics

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

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; Mo = Month; Mort = Mortality; NDI = National Death Index; PD = Parkinson's Disease; SSA = Social Security Administration; TCE = Trichloroethylene; US = United States; Yr = Year.
(a) Bove *et al.* (2014b) evaluated exposures at CL and health outcomes in Marines and Navy personnel using similar methods to those used in Bove *et al.* (2014a). There were < 5 cases of PD observed so they did not evaluate associations in analyses of Marines and Navy personnel.
(b) Median age from start to end of follow-up (Bove *et al.*, 2014a).
(c) Ages and population sizes are reflective of Marines, Navy personnel, 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 (ATSDR, 2013b), some of whom were included in this analysis (ATSDR, 2018b).
(d) Median age range at survey or death (ATSDR, 2018b).

Table H.2 Vinyl Chloride and PD Cohort Study Results

Study	Statistical Analysis							
	Reference Group	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{Trend}	Covariates Adjusted For
Mortality								
Bove *et al.* (2014a)	CL civilian employees with < median exposure	HR	**CL Civilian Employees**					
			Maximum cumulative exposure level with 10-yr lag[a]					
			≥ Median	4	–	2.81 (0.23-34.11)	–	Age, sex, race, blue- or white-collar occupation, and education
Incidence								
ATSDR (2018b)	CP Marines & Navy personnel	OR	**CL Marines & Navy Personnel**					
			Cumulative exposure level[b]					
			Low	41	–	0.86 (0.47-1.59)	–	Sex
			Medium	34		0.87 (0.46-1.62)		
			High	3		0.29 (0.08-1.00)		
	CL Marines & Navy personnel with low exposure		Medium	34		1.00 (0.63-1.59)		
			High	3		0.33 (0.10-1.09)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mo = Month; OR = Odds Ratio; PD = Parkinson's Disease; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compounds; US = United States; Yr = Year.
– = Not Reported.
Bold text indicates statistical significance.
(a) To evaluate exposure-response relationships, Bove *et al.* (2014a) evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were positive, and the coefficient for continuous untransformed cumulative exposure was statistically significant (beta coefficient **=** 0.0129, 95% CI: 0.0063-0.0253).
(b) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses. Categorized levels 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).

Attachment I

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*

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Prueitt, RL; Li, W; Zhou, J; Goodman, JE. 2021. "Systematic Review of the Association Between Long-Term Exposure to Ambient Fine Particulate Matter and Mortality." Abstract/Poster: 2304/P180. Presented at the Society of Toxicology (SOT) 60th Annual Meeting & ToxExpo, held virtually March 21-26.

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Bailey, LA; Kerper, LE; Goodman, JE. 2016. "Occupational Exposure Level for Manganese in Welding Fumes Based on the Best Available Science." Presented at the Manganese 2016 Conference: Manganese Health Effects on Neurodevelopment & Neurodegenerative Diseases, New York, NY, September 25-28.

Goodman, JE; Zu, K; Tao, G; Rhomberg, LR. 2016. "Evaluation of Occupational Benzene Exposure and Leukemia Mortality: A Lifetable Analysis of the Pliofilm Cohort." Presented at the Epidemiology Congress of the Americas 2016 Annual Meeting, Miami, FL, June 21-24.

Zu, K; Tao, G; Goodman, J. 2016. "Pleural plaques and lung function in the Marysville worker cohort: A re-analysis." Presented at the Epidemiology Congress of the Americas 2016 Annual Meeting, Miami, FL, June 21-24.

Lange, SS; Tao, G; Rhomberg, LR; Goodman, JE; Dourson, ML; Honeycutt, ME. 2016. "Dose Response Curves Derived from Clinical Ozone Exposures Can Inform Public Policy." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Zu, K; Lemay, JC; Zhang, J; Goodman, JE. 2016. "A Hazard and Risk Assessment of Phenoxyethanol in Children's Personal Care Products." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Prueitt, RL; Cohen, JM; Goodman, JE. 2016. "Evaluation of Atherosclerosis as a Mode of Action for the Cardiovascular Effects of Particulate Matter." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Seeley, MR; Goodman, JE. 2016. "Evaluation of Nitrogen Dioxide and Airway Hyper-responsiveness." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Zu, K; Loftus, CT; Goodman, JE. 2015. "Non-Hodgkin's Lymphoma and 2,4-dichlorophenoxyacetic Acid: A Meta-analysis." Poster No. 022. Presented at the Society for Epidemiological Research 48th Annual Meeting, Denver, Colorado, June 19, 2015.

Rhomberg, LR; Mayfield, DB; Goodman, JE; Butler, EL; Nascarella, MA; Williams, DR. 2015. "Quantitative Cancer Risk Assessment for Occupational Exposures to Asphalt Fumes During Built-up Roofing Asphalt (BURA) Operations." Presented at the INRS 2015 Occupational Health Research Conference, Nancy, France, April 8-10.

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 J

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