Exhibit 67

General Causation Expert Report of Steven B. Bird, MD

Bladder Cancer

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Contents

I. Qualifications 5
II. Methodology 6
III. "As Likely as Not" Standard 7
IV. Summary of Opinions 8
V. The Chemicals Found at Camp Lejeune That CAN Cause Cancer 12
A. The chemicals at Camp Lejeune Generally 12
1. Chlorinated ethylene organic solvents (TCE, PCE, vinyl chloride, and their relatives) 13
B. The particular carcinogens present at camp Lejeune 14
1. Perchloroethylene (PCE) 14
2. Trichloroethylene (TCE) 15
3. Benzene 15
4. Vinyl Chloride 16
C. Mechanisms of toxicity 17
1. PCE and bladder cancer 17
2. TCE and bladder cancer 17
3. Benzene and bladder cancer 18
4. Vinyl chloride and bladder cancer 19
VI. Chemical Contamination in the Water at Camp Lejeune Spanned Decades 20
A. Hadnot Point: TCE Contamination 20
B. Hadnot Point: Benzene Contamination 21
C. Hadnot Point: PCE CONTAMINATION 21
D. Tarawa Terrace: TCE Contamination 22
E. Tarawa Terrace: PCE Contamination 22
F. Holcomb Boulevard 23
G. Risk Assessments 23
1. Risks based on CREG limits underrepresent actual cancer risk 23
2. Theoretical risks are grounded in conservative assumptions 24
3. Human epidemiology provides superior evidence 24
4. The limited relevant data from risk assessment in this case supports the conclusion that the toxins at Camp Lejeune are hazardous to human generally and can cause bladder cancer 25

VII. Routes of Exposure to These Chemicals 26
A. In general 26
B. Absorption via ingestion 28
1. TCE 28
2. PCE 29
3. Benzene 30
4. Vinyl chloride 30
C. Absorption via inhalation 31
1. TCE 31
2. PCE 31
3. Benzene 32
4. Vinyl chloride 32
D. Absorption via dermal exposure. 33
1. TCE 33
2. PCE 33
3. Benzene. 34
4. Vinyl chloride. 34
VIII. Literature Review 34
A. Occupational Studies 34
B. Water-Contamination Studies 35
1. Aschengrau et al., 1993, Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts 35
C. Evidence from Camp Lejeune studies Confirms That These Chemicals Cause Bladder Cancer at Detected Concentrations 37
1. ATSDR 2018 Study: Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune 38
2. Bove 2024b Study: *Cancer Incidence Among Individuals Exposed to Contaminated Drinking Water at Camp Lejeune* 39
3. Rosenfeld 2024 Study: *Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955 to 1987* 40
IX. Other Relevant Considerations 41
A. Carcinogenic Latency 41
B. Additive and Synergistic Effects of Solvents and Toxins 41

X. Bradford Hill Analysis 44
A. TCE 44
B. PCE 46
C. Benzene 48
D. Vinyl Chloride 50
E. TVOC 52
XI. Conclusion 54

I. QUALIFICATIONS

I earned my Bachelor of Science degree in biology cum laude in 1991 from Yale University, where I was named a Yale University Richter Fellow. I worked in the laboratory of Professor Sidney Altman, Dean of Yale College and winner of the 1989 Nobel Prize in Chemistry. I was awarded my Doctor of Medicine degree by Northwestern University in 1995 and was also elected to the Alpha Omega Alpha national medical honor society (generally awarded to the top 10% of medical students nationally). Following medical school, I gained post-graduate training through residencies with the Naval Hospital San Diego (surgery) and the University of Massachusetts Medical School (emergency medicine). In addition, I completed a two-year fellowship in medical toxicology at the University of Massachusetts Medical School in 2004.

I began my independent clinical career in the Department of Emergency Medicine at the University of Massachusetts Medical School in 2002. I was promoted to Assistant Professor of Emergency Medicine in 2004, to Associate Professor in 2010, and to full Professor in 2016. In addition, I served as Program Director of the Emergency Medicine Residency Program and as Vice Chair of Education for the Department of Emergency Medicine at the University of Massachusetts Medical School from 2011 to 2019. I am currently the Division Chief of Medical Toxicology at the UMass Chan Medical School and UMass Memorial Health. I work as an Attending Emergency Physician at UMass Memorial Medical Center and Clinton Hospital. I am actively involved with numerous professional committees within the UMass Chan Medical School and its Department of Emergency Medicine and Division of Medical Toxicology, and in national and international scientific organizations, such as the Society for Academic Emergency Medicine, the American College of Medical Toxicology, and the American College of Emergency Physicians. I served on the Board of Directors of the Society for Academic Emergency Medicine from 2014-2020 and was President of the Society from 2018-2019. Additionally, I was formerly President of the Medical Staff of UMass Memorial Healthcare.

During my professional career, I have received several awards, including the Navy and Marine Corp Achievement Medal, the Outstanding Contribution to Medical Toxicology Research by the American College of Medical Toxicology; the Society for Academic Emergency Medicine ("SAEM") Best Resident Basic Science Presentation Award, the SAEM New England Regional Research Directors Excellence in Research Award, the teaching award (twice) from the UMass Emergency Medicine Residency, and a Young Investigator Award from the Society for Academic Emergency Medicine.

I am a reviewer for several scientific journals, including the Journal of Medical Toxicology; Clinical Toxicology; Annals of Emergency Medicine; Academic Emergency Medicine; Toxicology; the New England Journal of Medicine; and JAMA. I currently serve on the Editorial Board of Academic Emergency Medicine and was a founding editorial board member of the Journal of Medical Toxicology. I am certified by the American Board of Emergency Medicine and the American Board of Medical Toxicology. I currently hold a license to practice medicine in Massachusetts. In my practice of emergency medicine medical toxicology, I evaluate people exposed or potentially exposed to a variety of substances on a daily basis. In my review of this

case, I utilized scientifically valid and reliable methods to perform my research, followed by a differential etiology methodology and consideration of the weight of the evidence and the Bradford-Hill viewpoints.

II. METHODOLOGY

In my search of the medical and scientific literature, I conducted many searches of the PubMed database, using terms including (but not exclusive to):

> (TCE OR PCE OR benzene OR vinyl chloride OR trichloroethylene OR tetrachloroethylene OR perchloroethylene) AND (bladder OR transitional cell OR urothelial) AND (cancer OR carcinoma)

I also performed numerous searches using Google Scholar, which gives quick access to full-text articles as well as an immediate list of citing articles for that manuscript. In order to identify even more articles, I reviewed the articles cited in the manuscripts I reviewed. I also reviewed toxicology and medical toxicology textbooks, as well as chemical toxicity databases such as the Hazardous Substances Data Bank, United States Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS), and Agency for Toxic Substances and Disease Registry (ATSDR). In addition, I reviewed the records and other materials that counsel for Plaintiffs sent to me.

My methodology for reviewing literature in this case is identical to my methodology when seeing a patient and that which I teach residents and fellows.

After exposure to a toxin, people will often present at the emergency department. In my practice of emergency medicine and medical toxicology, I evaluate people exposed or potentially exposed to a variety of substances on a daily basis. In my review of this case, I utilized scientifically valid and reliable methods to perform my research, followed by consideration of the weight of the evidence and the Bradford-Hill viewpoints.

Even though some of the epidemiological results presented in this report are not statistically significant under traditional methods, they are important and relevant information with regards to causation where the standard is equipoise because the concept of equipoise refers to genuine uncertainty within the expert medical community. Many of the results are very nearly statistically significant and are clearly *not* directed towards a decrease in occurrence or risk of the cancers. Furthermore, the use of traditional statistical significance does not capture or account for biological plausibility of cancer causation. Likewise, relying on traditional statistical significance ignores known carcinogenic properties of a substance. Lastly, biostatisticians have largely abandoned the dichotomous interpretation of statistical significance (i.e., significant vs. non-significant) and instead focus on the estimation of effect sizes.

I am being compensated at a rate of $600 per hour for review and report writing and $1,000 per hour for deposition or trial testimony.

I reserve the right to supplement this report.

III. "AS LIKELY AS NOT" STANDARD

The statute at issue in this case, the Camp Lejeune Justice Act (CLJA), states:

> (2) Standards – To meet the burden of proof described in paragraph (1), a party shall produce evidence showing that the relationship between exposure to the water at Camp Lejeune and the harm is –
>
> (A) Sufficient to conclude a causal relationship exists; or
>
> (B) sufficient to conclude a causal relationship is at least as likely as not.

This standard has significant implications for the analysis at issue in this report. The standard and its language have application in the field of toxicology, epidemiology, and other similar sciences. The determination of a causal relationship is naturally different under a standard that requires a proof "more likely than not," as compared to a standard that requires a proof "as likely as not."
To this point, ATSDR (2017) in its assessment of the evidence, utilized differing causality standards in the context of assessing the causal relationship between the toxins in the drinking water at Camp Lejeune and different diseases. Specifically, ATSDR utilized the following causality standards:

> Sufficient evidence for causation: the evidence is sufficient to conclude 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.
>
> Equipoise and above evidence for causation: 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., $\leq$ 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 bias 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.

Similar standards have been used in other areas of toxicology, epidemiology and by other governmental bodies. For example, as ATSDR notes, the classification scheme used in the 2017 assessment of the evidence is one "recommended by an IOM panel that reviewed the VA's presumptive disability decision-making process for veterans (IOM 2008).

This classification scheme is consistent with my many years of experience in these fields of science and also based on sound scientific and methodological grounds. It therefore informs an analysis of causality that is necessarily based upon toxicology, epidemiology and other similar sciences.

IV. SUMMARY OF OPINIONS

In my view, the water at Camp Lejeune, which was contaminated with significant levels of benzene, trichloroethylene (TCE), perchloroethylene (PCE), and vinyl chloride, causes bladder cancer. Each of these toxins has meaningful scientific evidence supporting its causality to bladder cancer. This is especially true given the reduced standard at issue in this litigation, an as likely as not standard or equipoise.

Benzene, TCE, and vinyl chloride are widely acknowledged carcinogens—all classified as IARC Group 1 carcinogens, meaning the agency believes "a causal relationship has been established between exposure to the agent and human cancer." [IARC Monograph 120, 2018]. Epidemiology has further indicated that "the estimated exposure to trichloroethylene was significantly associated with an increased risk of bladder cancer." [Hadkhale K. Int J Cancer 2017;140:1736-46]. And that "bladder cancer risks were increased among those ever exposed to benzene." [Xie S. J Exposure Sci Environ Epidemiol 224;34:546-53]. Vinyl chloride has been evaluated by IARC and is classified as a Group 1 carcinogen based on increased risks for angiosarcoma of the liver and hepatocellular carcinoma [IARC Monograph 100F, 2012].

PCE is classified as IARC Group 2A "probable human carcinogens" - this classification was based on PCE's association with bladder cancer specifically. [IARC Monograph 106, 2014] Likewise, the EPA has determined PCE is "likely to be carcinogenic to humans by all routes of exposure based on suggestive evidence in epidemiological studies and conclusive evidence" in animal studies. [EPA. Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4), 2012].

ATSDR goes a step further and "decided to adopt a different position from that currently held by EPA and IARC and conclude that there is **sufficient evidence for causation for PCE and bladder**

cancer." [ATSDR Assessment of the Evidence for the Drinking Water, 2017 at 95]. ATSDR came to this conclusion after determining "the epidemiological studies provide sufficient evidence for causation and are consistent with the mechanistic information that certain genetic polymorphisms may enhance the production of genotoxic PCE metabolites in the bladder via the GSH conjugate pathway." [ATSDR Assessment of the Evidence for the Drinking Water, 2017 at 95]

It is therefore unsurprising that "contaminated drinking water at Camp Lejeune," which contained not only PCE, but all four carcinogenic chemicals, "was associated with increased risk in both Marines and civilian employees for bladder cancer." [ATSDR. Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune, April 2018 – hereafter referred to as the ATSDR 2018 Morbidity Report]. "[I]ndividuals who spent time on the base" have "a high risk" of contracting cancer, including specifically "bladder cancer." [ATSDR 2018 Morbidity Report].

In addition, I have been asked to evaluate the levels of exposure to these chemicals that have been identified in scientific literature to be hazardous to human beings generally. Numerous studies provide evidence of specific levels of exposure—some of which align with the contamination observed at Camp Lejeune—that are associated with increased risks for bladder cancer.

Given the known facts from Camp Lejeune (e.g.: how much of each contaminant was in the water; how much water was utilized on base; and how long a person was generally housed on-base), it is possible to then calculate a person's exposure to the chemicals. I evaluated the literature and calculated the exposure of Camp Lejeune personnel to the water contaminants in order to determine if a person would have been exposed to enough of the chemicals to cause (to an as likely as not standard) their cancer. Below are the amounts of the Camp Lejeune water contaminants that have been shown to cause bladder cancer. Therefore, it is my opinion to a reasonable degree of medical certainty that any individual with exposure to anyone of these chemicals at the level (or higher than the levels) identified below, as likely as not, were at an increased risk of bladder cancer. However, given inherent limitations to epidemiologic data (principally that the data are population-based and not based on any one individual), the exposure quantities below should not be interpreted as floors below which cancer does not occur:

1. **Cumulative exposure to 27-44 mg of PCE**: 1. Aschengrau A, Ozonoff D, Paulu C, et al. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. *Arch Environ Health*. 1993;48(5):284-292.

2. **Cumulative exposure to less than 110 ppb-months of TCE**: Agency for Toxic Substances and Disease Registry (ATSDR). *Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune*. April 2018.

3. **Cumulative exposure to less than 36 ppb-months of PCE**: ATSDR, 2018.

4. **Cumulative exposure to 110 – 11,030 ppb-months of TCE**: ATSDR, 2018.

5. **Cumulative exposure to 36 - 711 ppb-months of PCE**: ATSDR, 2018.

6. **Cumulative exposure greater than 11,030 ppb-months of TCE**: ATSDR, 2018.

7. **Cumulative exposure greater than 711 ppb-months of PCE**: ATSDR, 2018.

8. **1098 ppb-months of TCE:** Bove FJ. Cancer Incidence among Marines and Navy Personnel and Civilian Workers Exposed to Industrial Solvents in Drinking Water at US Marine Corps Base Camp Lejeune: A Cohort Study. *Environ Health Perspect* 2024b;132;10.

9. **45 ppb-months of PCE**: Bove 2024b Cancer Incidence Study

10. **15 ppb-months of benzene:** Bove 2024b Cancer Incidence Study

11. **18 ppb-months of vinyl chloride**: Bove 2024b Cancer Incidence Study

12. **285 ppb-months of TVOC** (Tarawa Terrace) or **1,224 ppb-months of TVOC** (Hadnot Point): Bove 2024b Cancer Incidence Study

It is also worth noting that the ATSDR, in its 2017 Assessment, stated that the "evidence from the epidemiological studies included in this assessment is not sufficeint to contradict this minimum duration," i.e., 30 days on base. My understanding of the Justice Act is that all Plaintiffs in this case were on the Camp Lejeune base for at least 30 days.

The report continued, "Moreover the results from the Camp Lejeune mortality studies suggest that a 30 day minimum duration requirement may be appropriate since elevated risks for some of the diseases evaluated were observed for exposure durations of 1-3 months. These results should not be surprising given that the levels of TCE, PCE and vinyl chloride measured or estimated in the drinking water systems at Camp Lejeune considerably exceeded their respective MCLs."

The evidence in this case mirrors one of the oldest examples of epidemiology detecting a causal association. In the mid-1800s, British physician John Snow compared the rates of cholera in people who drank water from a company who drew its water from "comparatively clean, Thames water upstream from London" and another company who drew its water from "downstream of London and therefore contaminated with sewage." [Rothman K. Modern Epidemiology, 4th Edition, 2021]. The cholera rates were higher in households who drank water from the downstream company, thereby demonstrating convincingly that contaminated water was causing the cholera.

The evidence for Camp Lejeune largely relies on similarly elegant "natural experiment" designs. The studies looked at the rates of bladder cancer in areas of high contaminant concentrations and compared those rates to areas of lower contaminant concentrations. Some of the studies did so for Camp Lejeune itself, comparing rates of bladder cancer in personnel stationed there to the bladder cancer rates in personnel stationed at bases where the water was not contaminated. Just as the differential cholera rates between the pumps demonstrated a causal relationship between cholera

and the water in 1800s London, the differential bladder cancer rates between Camp Lejeune and other marine bases demonstrates a causal relationship here.

The significant evidence from the above valid and methodologically sound studies establishes that exposure to the levels of the toxins in the drinking water at Camp Lejeune were hazardous to human beings generally and are known causes of bladder cancer. Much of the evidence related to Camp Lejeune stems from sophisticated natural experiment designs, particularly research comparing bladder cancer incidence rates in regions with higher and lower or negligible exposure. Some studies specifically examined bladder cancer among personnel stationed at Camp Lejeune compared to those at bases with uncontaminated water supplies.

This body of evidence provides a foundation for analyzing the levels of chemical exposure generally harmful to humans. Numerous studies document elevated bladder cancer hazards associated with varying levels of exposure to these chemicals. Observing increased hazards and risks at these levels demonstrates that such exposures are clearly capable of causing bladder cancer, even though it is likley that lower levels are also hazardous and pose these same risks.

A limitation in defining hazardous levels of exposure to TCE, PCE, benzene, or vinyl chloride is the absence of randomized controlled trials. Determining precise thresholds would require unethical and impractical long-term studies exposing human participants to these chemicals and monitoring their health outcomes over decades. Instead, there are data from observational studies that estimate exposure levels and assess whether affected populations show higher-than-expected bladder cancer rates.

It is uncommon for humans to be exposed to environmental chemicals in a way that allows for a precise assessment of negative effects. Epidemiological evidence often reflects gaps in toxicological prevention or regulatory oversight. However, research into TCE, PCE, benzene, and vinyl chloride—especially federal investigations into Camp Lejeune—offers robust data on the consequences of exposure to these chemicals at various concentrations and durations. These data provide compelling evidence that the water contamination at Camp Lejeune were at levels known to cause bladder cancer.

While epidemiological data often focuses on specific dose ranges where elevated risks have been observed, these should not be interpreted as definitive minimum thresholds below which no hazard exists. Rather, these ranges reflect only the levels studied. It is indeed very likely that lower concentrations also contribute to bladder cancer risk. For carcinogens such as TCE, PCE, benzene, and vinyl chloride, even minimal exposure is known to be sufficient to trigger genetic mutations or other biological changes that can lead to cancer. This is consistent with the generally-accepted scientific understanding that some carcinogens may not have a threshold below which exposure is entirely safe.

The available data indicates that the levels of chemical exposure at Camp Lejeune were hazardous to humans and are known to cause bladder cancer. Epidemiological findings clearly demonstrate increased bladder cancer hazards at these levels and provides strong support that levels lower than those found specifically in the epidemiology are also hazardous to humans generally and are

known to cause bladder cancer.

In my opinion, the water at Camp Lejeune more likely than not causes bladder cancer—comfortably exceeding the at least as likely standard set forth by Congress. Furthermore, I believe that the quantitative risk of bladder cancer from exposure to the combination of TCE, PCE, vinyl chloride, and benzene is more likely than not additive or even higher.

V. THE CHEMICALS FOUND AT CAMP LEJEUNE THAT CAN CAUSE CANCER

The major drinking-water contaminants of interest at Camp Lejeune are volatile organic chemicals (VOCs): mainly trichloroethylene (TCE) and tetrachloroethylene (also known as perchloroethylene or PCE), but also benzene and vinyl chloride (as well as other chemicals that I will not address in this report). All those except benzene are halogenated, short-chain aliphatic hydrocarbons (halocarbons) - benzene is an aromatic hydrocarbon.

A. THE CHEMICALS AT CAMP LEJEUNE GENERALLY

To understand how exposure to the contaminated water at Camp Lejeune can cause bladder cancer, it's useful to consider how the underlying chemicals present can affect human health generally. TCE, PCE, benzene, and vinyl chloride are all organic solvents.

A solvent is a substance that dissolves another substance. While water is the most common solvent, a number of substances (especially those with oils as part of their make-up), do not dissolve well in water. Organic solvents are a class of solvents made up of chemical compounds - primarily carbon and hydrogen (hence the term "hydrocarbon") - sometimes combined with other elements (e.g., chlorine), are often used to aid this process. These solvents dissolve fat and oil easily. In turn, organic solvents are also able to dissolve in fat.

As a result of their ability to dissolve in fat (known as lipophilicity), organic solvents can permeate the human body. For example, organic solvents are uniquely able to affect the brain and nervous system by easily crossing the "blood brain barrier." This natural protective barrier separates circulating blood from the fluid from the brain, isolating the central nervous system from the rest of the body. Because of the substantial fatty component in skin, organic solvents are also easily absorbed through the skin.

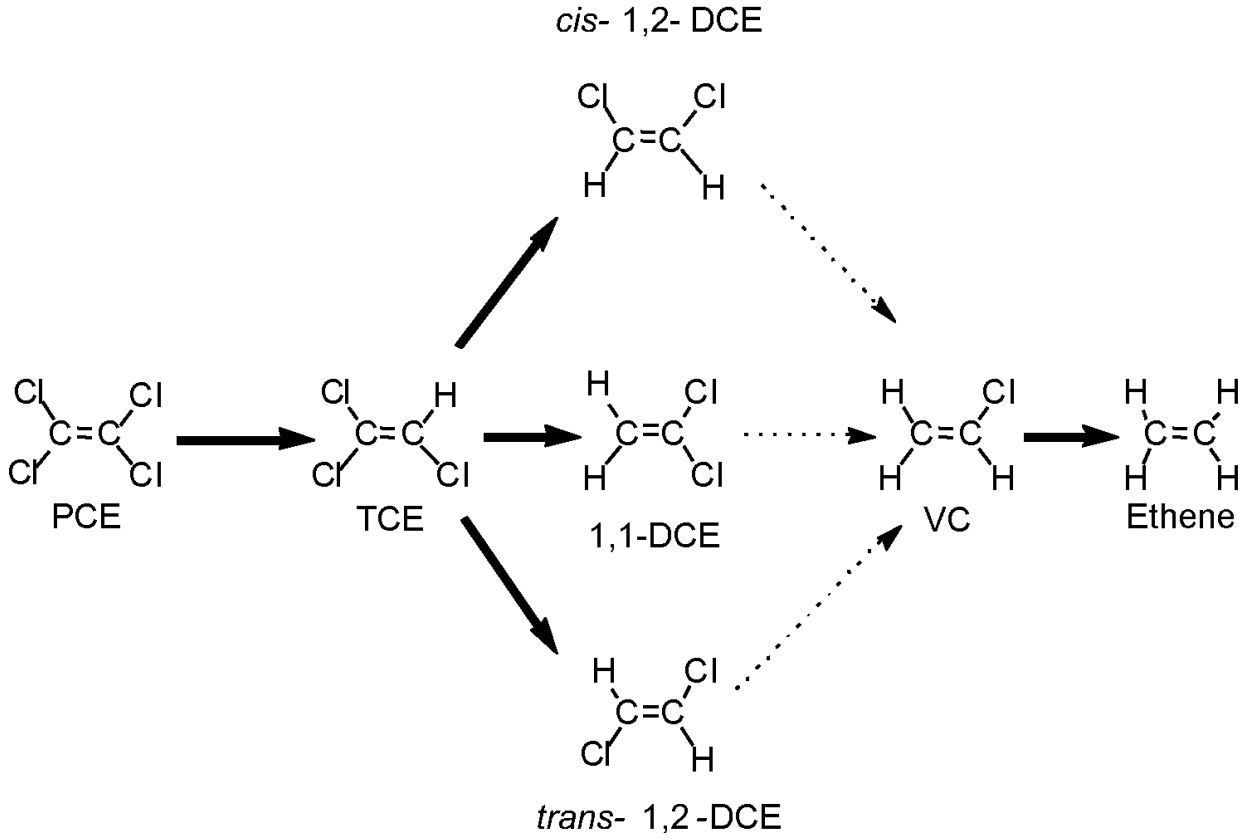
Many organic solvents are volatile (easily evaporated), leading to possible exposure through inhalation. Where these solvents are present in the water supply, they can easily move into the air under conditions such as showering, dishwashing, or toilet flushing. They can also enter homes through groundwater in a process known as vapor intrusion.

Because TCE, PCE, benzene, and vinyl chloride are organic solvents, their presence in a primary water source, like at Camp Lejeune, can result in exposure through ingestion of food and water,

inhalation of indoor air, and absorption through the skin. It has been estimated that exposure to occupants through the air and skin from the drinking water source alone is roughly equal to, or may even exceed, exposure from ingestion.

1. Chlorinated ethylene organic solvents (TCE, PCE, vinyl chloride, and their relatives)

A subcategory of organic solvents is chlorinated volatile organic compounds (CVOCs), which can be divided into three groups based on their structures (methane, ethane, and ethylene). Of particular relevance in this case is the third subclass: chlorinated ethenes (also known as chlorinated ethylene). Chlorinated ethenes share on a common backbone: a variation on the underlying structure of the hydrocarbon known as ethylene. Ethylene is composed of two carbon atoms, connected by a double bond. Each carbon has two more places to connect other atoms. If all four connections are to hydrogen atoms, the result is ethylene (far right, figure below). Chlorinated ethenes result when a chlorine atom replaces at least one of the hydrogens.



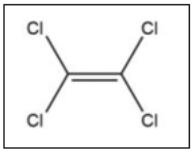
In PCE, two chlorine atoms attach to each carbon atom, displacing all of the hydrogens completely. The other chlorinated ethenes are sometimes referred to as PCE's "daughter products" because through reductive dechlorination, PCE will degrades to TCE, then to a form of dichloroethylene (DCE), to vinyl chloride, and finally to ethylene. In turn, ethylene can degrade to carbon dioxide and water.

While very little data exists on how dichloroethylene affects humans and most regulatory bodies have not evaluated its carcinogenicity "due to lack of information," [ATSDR DEC ToxFAQ 2023, at 2], the National Toxicology Program classifies DCE as "reasonably anticipated to be a human carcinogen" due to studies in experimental animals. [National Toxicology Program 15th Report on Carcinogens, 2021]. This is consistent with PCE's other daughter products: TCE and vinyl chloride. [IARC Monograph 106, 2014 at 189] ("There is sufficient evidence in humans for the carcinogenicity of [TCE]"); [IARC Monograph 97, 2008 at 425] ("There is sufficient evidence in humans for the carcinogenicity of vinyl chloride."). PCE itself is classified as "probably carcinogenic to human." [IARC Monograph 106, 2014 at 329].

The closely related chemical structure of chlorinated ethenes, specifically the three present at Camp Lejeune, does not mean they cause the same biological effects but can inform a deeper understanding of the scientific literature, especially to the degree there are limits to current research.

B. THE PARTICULAR CARCINOGENS PRESENT AT CAMP LEJEUNE

1. Perchloroethylene (PCE)



Perchloroethylene (also known as tetrachloroethylene) is widely known for its wide use in the dry-cleaning industry, but it has had other uses in industry. In the 1950s, roughly 80% of PCE was used for dry-cleaning; today, PCE use has been phased out in some states, and much less is used in dry-cleaning. Other industrial uses of PCE include as a degreaser and chemical synthesis intermediate.

PCE is classified by every regulatory body as a probable human carcinogen. In 2014, IARC classified PCE as probably carcinogenic to humans (Group 2A) based upon sufficient evidence in animals and limited evidence in humans [IARC 2014 at 329]. Similarly, in 2012 the EPA declared that PCE is "Likely to be Carcinogenic to Humans" by all routes of exposure. [EPA. Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4), 2012]. Furthermore, the National Toxicology Program (NTP) has opined that PCE "is reasonably anticipated to be a human carcinogen." [NTP 15th Report on Carcinogens, 2021].

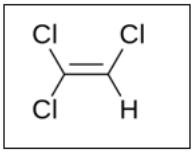
These classifications are based on PCE's association with bladder cancer in particular. "The bladder has been identified as a target organ for tetrachloroethylene-induced carcinogenesis." [IARC 2014]. Extensive reviews of the "epidemiologic evidence provides a pattern associating tetrachloroethylene exposure and several types of cancer, including bladder cancer." [EPA 2012]; [IARC 2014] ("Positive associations have been observed for cancer of the bladder.").

While substantial portions of the human epidemiology regarding PCE and bladder cancer concern occupational exposure of laundry and dry-cleaning workers, thorough meta-analysis found the increased risk of bladder cancer in the dry cleaners' occupational studies could not be explained by confounding due to tobacco smoking. [Vlaanderen J. Environ Health Perspect 2014;122:661–

6]. Furthermore, Guyton *et al.* found that the epidemiological data was sufficiently "suggestive of a causal association." [Guyton KZ. Environ Health Perspect 2014;122:325–34].

The 2012 EPA report on PCE and bladder cancer concluded that ". . . the pattern of results from this collection of studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude. The effect estimates from four of the five studies with the relatively high quality exposure-assessment methodologies provide evidence of an association, with relative risks of 1.44 to 4.03." [EPA 2012]. Furtermore, the EPAC concluded that "Confounding by smoking is an unlikely explanation for the findings, given the adjustment for smoking by Pesch *et al.* (2000a) and other case-control studies." [EPA 2012 at 4-97].

2. Trichloroethylene (TCE)

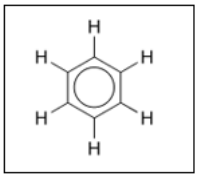


TCE is a human-made, colorless, volatile liquid chemical that is used as a solvent and in many other applications. TCE is used as a solvent to remove grease from metal, as a paint stripper, and in the production of other chemicals. It can also be found in some household products, such as cleaning wipes, paint removers, and adhesives. TCE is a volatile organic compound (VOC) that is highly persistent in the environment, contaminating soil and groundwater, as occurred at Camp Lejeune.

The scientific community agrees that TCE is carcinogenic. IARC classifies it as a known human carcinogen, citing "sufficient evidence in humans for the carcinogenicity of trichloroethylene" [IARC 2014 at 189]. The EPA concurs, describing TCE as carcinogenic to humans through all exposure routes

Hadkhale *et al.* studied occupational exposure to solvents (including TCE) in Nordic countries. Their utilized the Nordic Occupational Cancer (NOCCA) database, which included 113,343 cases of bladder cancer and 566,715 controls, and linked occupational titles to a job exposure matrix to estimate cumulative exposures. The study identified a statistically significant increased risk of bladder cancer associated with occupational exposure to TCE. Specifically, the HR for TCE exposure was 1.23 (95% CI 1.12-1.40) when comparing high exposure levels to no exposure. This indicates a 23% increased risk of bladder cancer among individuals with high occupational exposure to TCE compared to those with no exposure. The authors summarized that this finding indicates that "the estimated exposure to trichloroethylene was significantly associated with an increased risk of bladder cancer." [Hadkhale K. Int J Cancer 2017;140:1736-46].

3. Benzene



Benzene has historically been used as a degreaser of metals, a solvent for organic materials, in the chemical industry as an intermediate, and as an additive to gasoline. However, as the carcinogenicity of benzene became more widely recognized, its use has decreased. Benzene in the Camp Lejeune water is thought to have been present as a result of fuel leakage from storage tanks on base.

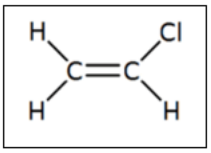
Every regulatory body agrees benzene is known human carcinogen. [IARC 2018; NTP 2021; EPA 2007]. While those classification are based on benzene ability to cause blood cancers, including leukemia, recent human epidemiology compellingly links benzene to bladder cancer. A 2023 cohort study suggested the "exposure to benzene may be associated with increased risk of bladder cancer." [Shala NK. Br J Cancer 2023;129:838–5 at 849]. Furthermore, the Xie 2024 case control study showed "[b]ladder cancer risks were increased among those ever exposed to benzene." Xie S. J Exposure Sci Environ Epidemiol 224;34:546-53]

Though this association was not identified in the ATSDR report or regulatory assessments of benzene, studies suggesting an association postdate all evaluations. Any causation analysis must include the most up-to-date research; "scientific enterprise must always remain open to reassessing the validity of past judgments as new evidence develops." [Ref Manual at 598].

Receptivity to emerging indications of a relationship between a chemical and disease is particularly important when that chemical is interacting with another of which there is stronger evidence of causation (i.e., PCE). An individual stationed at Camp Lejeune was exposed not simply to benzene, PCE, and TCE separately, but the combination of the chemicals within the water and with that, any synergistic effects that may occur. It's well accepted that an "individual's simultaneous exposure to more than one chemical may result in a response that differs from that which would be expected from exposure to only one of the chemicals." [Ref Manual at 673].

Another study which demonstrated an association between benzene and bladder cancer was conducted by Steineck *et al.* [Steineck G. Int J Cancer 1990;45:1012-7]. In their case-referent study of bladder cancer in Sweden they compared risk in 320 cases of bladder cancer to 363 controls. Exposure to benzene (any annual dose) gave a RR of 2.0 (95% CI 1.0-3.8), with the highest risk for the highest annual dose.

4. Vinyl Chloride



Vinyl chloride is a volatile compound used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC). Vinyl chloride has been detected at low concentrations in the air in the vicinity of vinyl chloride and PVC manufacturing plants and hazardous waste sites. Vinyl chloride has also contaminated groundwater from spills, landfills, and industrial sources. Vinyl chloride can also enter groundwater after being produced as a byproduct during the degradation of TCE and PCE.

According to IARC, "There is sufficient evidence in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcoma of the liver, and hepatocellular carcinoma. There is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride." [IARC Monograph 100F, 2012 at 451]. Similarly, the EPA has classified vinyl chloride as Group A "carcinogenic to humans." [EPA Hazard Assessment for Vinyl Chloride, report 75-01-4, January 2000]. The NTP has also found that vinyl chloride "is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans." [NTP 15th Report on Carcinogens, 2021].

C. MECHANISMS OF TOXICITY

1. PCE and bladder cancer

PCE causes bladder cancer through several mechanisms, primarily involving its metabolism and subsequent cellular effects [Cichocki JA. J Pharmacol Exp Ther 2016;359:110-26]

1. Metabolic Activation: PCE is metabolized in the liver via cytochrome P450-dependent oxidation and glutathione (GSH) conjugation pathways. The cytochrome P450 pathway generates metabolites such as trichloroacetic acid (TCA) and dichloroacetic acid (DCA), which are associated with carcinogenicity. The GSH conjugation pathway produces reactive metabolites that can cause DNA damage, particularly in the kidneys and bladder.

2. Genotoxicity: The metabolites of PCE, particularly TCA and DCA, can induce genotoxic effects, including DNA strand breaks and mutations. These genotoxic effects can lead to somatic mutations in bladder epithelial cells, contributing to carcinogenesis.

3. Oxidative Stress: PCE and its metabolites can generate reactive oxygen species (ROS), leading to oxidative stress. This oxidative stress can cause lipid peroxidation, protein oxidation, and DNA damage, further contributing to the initiation and progression of bladder cancer.

4. Cellular and Molecular Pathways: PCE exposure modulates the expression of genes involved in cancer induction, cell differentiation, cell-cycle progression, and apoptosis. For example, PCE has been shown to affect the expression of numerous genes which are involved in cell proliferation and apoptosis. These molecular changes can disrupt normal cellular homeostasis and promote malignant transformation.

2. TCE and bladder cancer

TCE is implicated in carcinogenesis primarily through its metabolites and their interactions with cellular components. The general mechanism involves several key processes [Cichocki JA. J Pharmacol Exp Ther 2016;359:110-26; Rusyn I. Pharmacol Ther 2014;141:1; Bruckner JV. Crit Rev Toxicol 1989;20:31-50]

1. DNA damage and mutagenicity: TCE and its metabolites, such as dichloroacetic acid and trichloroacetic acid, can induce DNA damage. This damage is often secondary to oxidative stress and the formation of DNA adducts, which can lead to mutations in oncogenes and tumor suppressor genes.

2. Epigenetic modifications: TCE exposure has been shown to cause epigenetic changes, including DNA hypomethylation and histone modifications. These changes can lead to the dysregulation of tumor-related genes, such as N-Ras, c-Jun, c-Myc, and c-Fos, promoting carcinogenesis.

3. Selective growth advantage: TCE exposure provides a selective growth advantage to cells with spontaneous mutations in oncogenes like K-ras and H-ras. This selective pressure can lead to clonal expansion of mutated cells, contributing to tumor development.

4. Inhibition of apoptosis: TCE and its metabolites can downregulate apoptosis, reducing the ability of the body to eliminate damaged or pre-cancerous cells. This inhibition of programmed cell death allows for the accumulation of genetic damage and the progression to malignancy.

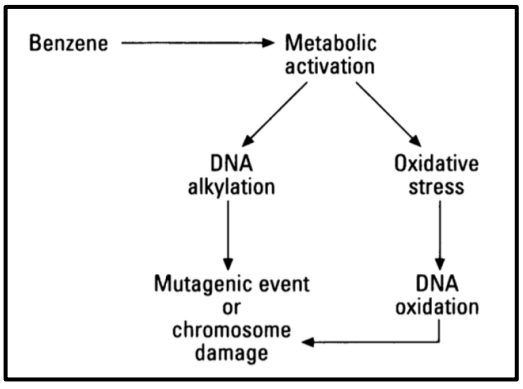
5. Oxidative stress and inflammation: exposure to TCE can lead to oxidative stress and inflammation, which are known to contribute to carcinogenesis. The production of reactive oxygen species (ROS) can cause further DNA damage and promote a pro-tumorigenic environment.

3. Benzene and bladder cancer

Benzene exposure leads to bladder cancer through several well-characterized mechanisms:

1. Metabolic activation and DNA adduct formation: Benzene is metabolized in the liver to reactive intermediates such as benzene oxide, phenol, and hydroquinone. These metabolites can be further processed to form DNA adducts, which are critical in initiating carcinogenesis. Specifically, benzene metabolites like N-acetylbenzidine can bind to DNA, forming adducts such as N'-(3'-monophospho- deoxyguanosin-8-yl)-N-acetylbenzidine (dGp-ABZ), which have been detected in bladder cells from exposed individuals. [Snyder R and Hedli C. Environ Health Perspect 1996;104:1165-71]

2. Oxidative stress and reactive oxygen species (ROS): Benzene metabolism generates ROS, which can cause oxidative damage to DNA, proteins, and lipids. This oxidative stress can lead to mutations and chromosomal aberrations, contributing to carcinogenesis.



In summary, benzene causes bladder cancer through mechanisms involving metabolic activation to DNA-damaging intermediates, induction of oxidative stress. These processes collectively contribute to the initiation and progression of bladder cancer.

4. Vinyl chloride and bladder cancer

Vinyl chloride contributes to the development of bladder cancer primarily through its metabolic activation and subsequent DNA damage. The key mechanisms include:

1. Metabolic Activation: Vinyl chloride is metabolized in the liver by cytochrome P450 enzymes, particularly CYP2E1, to form reactive intermediates such as chloroethylene oxide and chloroacetaldehyde. These metabolites are highly reactive and can form DNA adducts.

2. DNA Adduct Formation: The reactive intermediates of vinyl chloride, particularly chloroethylene oxide, form DNA adducts such as etheno adducts. These adducts are mutagenic and can lead to point mutations in critical genes involved in cell cycle regulation and apoptosis.

3. Mutagenesis and Carcinogenesis: The DNA adducts formed by vinyl chloride metabolites can cause mutations in proto-oncogenes and tumor suppressor genes. This mutagenic process can lead to the initiation and progression of carcinogenesis in the bladder epithelium.

4. Oxidative Stress and Inflammation: Vinyl chloride exposure also induces oxidative stress, which can further damage DNA and cellular components, contributing to carcinogenesis.

Vinyl chloride is metabolized by cytochrome P450 enzymes to form chloroethylene oxide, which can undergo spontaneous rearrangement to form chloracetaldehyde. Both of these chemicals are able to bind to DNA. Several DNA have been identified, some of which cause base-pair substitutions as well as frameshift mutations. [Kielhorn J. Environ Health Perspect 2000;108:579-88].

Vinyl chloride has been shown to cause genetic damage in many test systems including bacteria, yeast, human cells, other mammalian cells, and rodents exposed *in vivo*, as well as in exposed humans. The genetic damage included mutations, DNA damage, chromosomal aberrations, and sister chromatid exchange. Vinyl chloride caused mutations in bacteria with or without metabolic activation. However, its metabolites chloroethylene oxide and chloracetaldehyde were more potent mutagens than vinyl chloride itself. These results suggest that vinyl chloride may require mammalian metabolic activation in order to cause genetic damage in systems other than humans [Giri AK. Mut Res 1995;339:1-14].

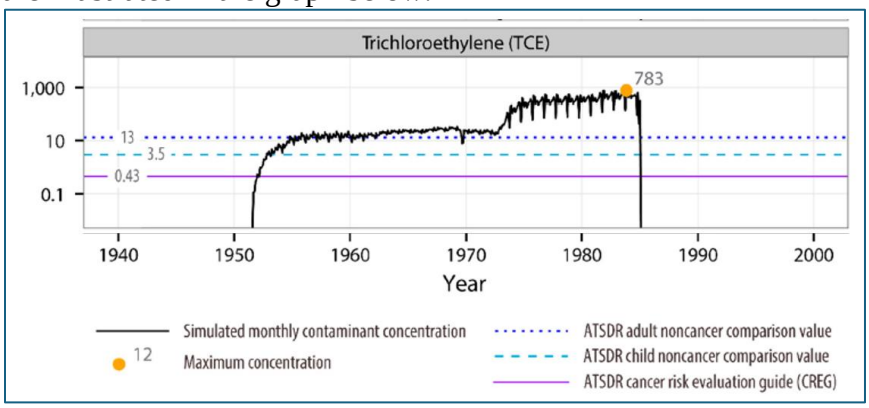
VI. CHEMICAL CONTAMINATION IN THE WATER AT CAMP LEJEUNE SPANNED DECADES

The ATSDR conducted mathematical modeling to simulate the contaminants in the water supplied to base housing and other facilities at Camp Lejeune. The modeling results revealed that water provided by the Tarawa Terrace and Hadnot Point Water Treatment Plants was contaminated with various levels of PCE, TCE, 1,2-tDCE (trans-1,2-dichloroethylene), vinyl chloride, and benzene between 1953 and 1987. Detailed monthly mean contaminant concentrations over time for Tarawa Terrace, Hadnot Point, and Holcomb Boulevard are documented in the ATSDR tables and were also provided to me in Appendices H1, J, and K of the October 25, 2024, Expert Report by Morris L. Maslia.

At the Tarawa Terrace Water Treatment Plant, simulated PCE levels peaked at an average of 183 µg/L per month, with a single measured high of 215 µg/L, both far above the EPA's current limit of 5 µg/L. These levels exceeded the limit between November 1957 and February 1987. At Hadnot Point, simulated TCE levels averaged a maximum of 783 µg/L per month, with a one-time high of 1,400 µg/L, during the period from August 1953 to December 1984. Hadnot Point also supplied contaminated water to the Holcomb Boulevard housing area continuously until June 1972, when the Holcomb Boulevard Water Treatment Plant began operations. After that, Hadnot Point intermittently provided water with TCE levels peaking at 32 µg/L before June 1972 and 66 µg/L between June 1972 and February 1985.

A. HADNOT POINT: TCE CONTAMINATION

At Hadnot Point, TCE concentrations ranged from 0 to 783 micrograms per liter, with a median level of 366 micrograms per liter. [Bove 2014a at 3]. The reconstructed concentrations in the water are illustrated in the graph below.



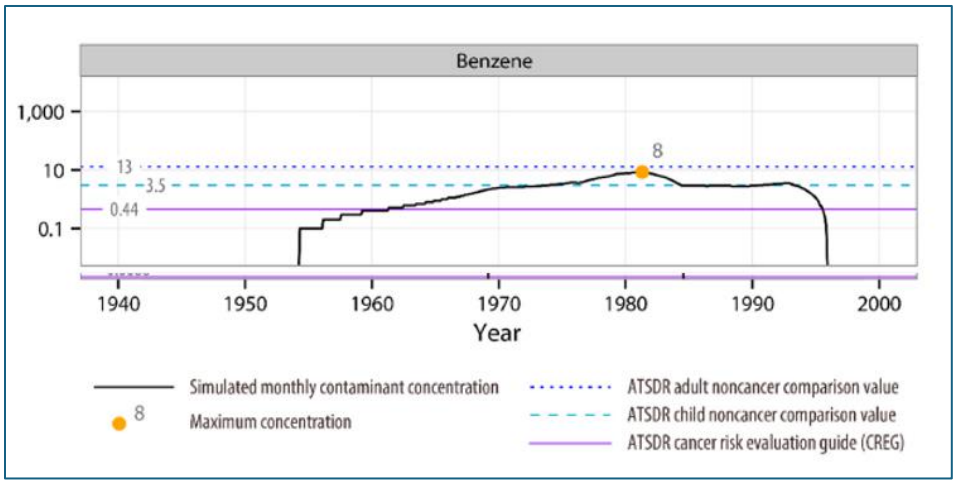
The graph illustrates that TCE concentrations at Hadnot Point consistently exceeded CREG level,[1] defined as the "concentrations of cancer-causing substance [that are] unlikely to result in an increase of cancer risk in an exposed population." [ATSDR PHA at 7]. For TCE, the CREG limit

[1] CREG refers to the Cancer Risk Evaluation Guide level developed by the ATSDR. [ATSDR PHA at 7].

is 0.43 ppb. With a maximum concentration of 783 ppb at Camp Lejeune, TCE levels exceeded the CREG limit by a factor of 1,820.

B. HADNOT POINT: BENZENE CONTAMINATION

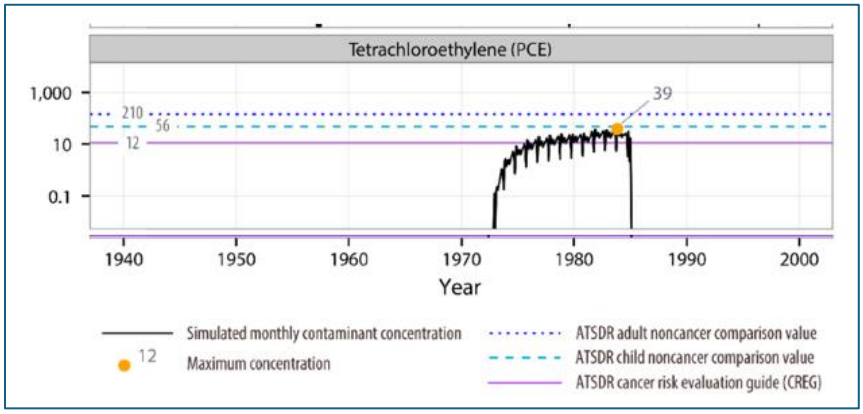
The reconstructed benzene concentrations in the water at Hadnot Point are illustrated in the graph below.



The graph shows that benzene levels consistently surpassed the CREG level of 0.45 ppb. The maximum benzene concentration recorded at Camp Lejeune was 8 ppb, exceeding the CREG limit by a factor of 17.

C. HADNOT POINT: PCE CONTAMINATION

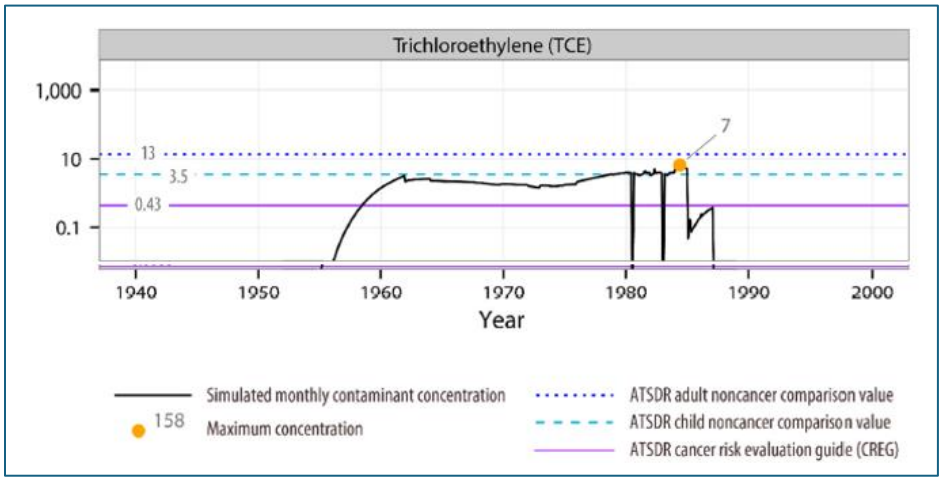
At Hadnot Point, the median monthly PCE contamination was 15 micrograms per liter. [Bove 2014a at 3]. The reconstructed concentrations in the water are illustrated in the graph below.



As shown, PCE concentrations at Hadnot Point regularly exceeded the CREG limit of 12 ppb. The maximum concentration of 39 ppb recorded at Camp Lejeune was more than three times the CREG limit.

D. TARAWA TERRACE: TCE CONTAMINATION

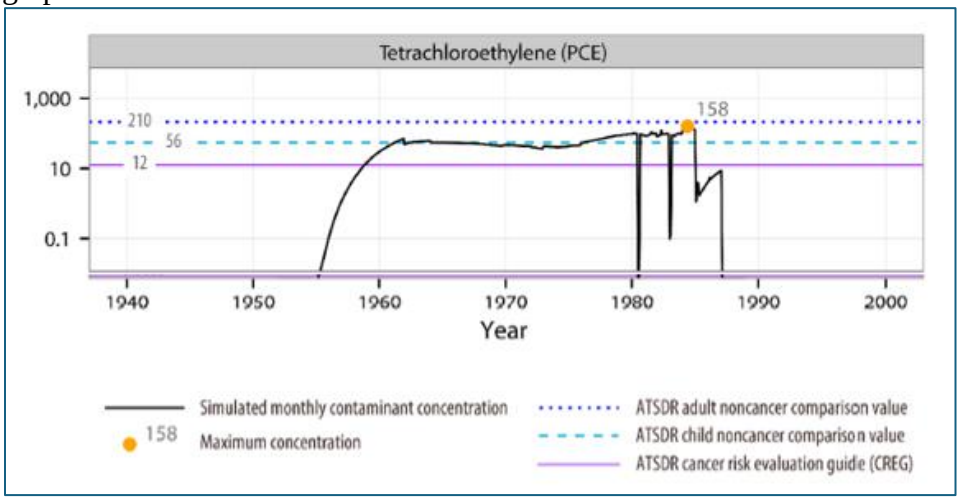
The reconstructed TCE concentrations in the water at Tarawa Terrace are shown below.



The graph reveals that TCE levels at Tarawa Terrace regularly exceeded the CREG limit of 0.43 ppb. The highest reconstructed concentration of 7 ppb at Camp Lejeune was more than 16 times the CREG limit.

E. TARAWA TERRACE: PCE CONTAMINATION

At Tarawa Terrace, concentrations of PCE ranged from 0 to 158 µg/liter, with a median of 85 µg/liter [Bove 2014a at 3]. The reconstructed concentrations in the water are illustrated in the graph below.



The graph indicates that PCE concentrations at Tarawa Terrace routinely surpassed the CREG limit of 12 ppb. The maximum concentration of 158 ppb was more than ten times the CREG limit, exceeding it by an order of magnitude.

F. HOLCOMB BOULEVARD

Holcomb Boulevard was also affected by the contamination. Before 1972, its water supply came from Hadnot Point water system, meaning the exposure analysis for Holcomb Boulevard aligns with that of those in Hadnot Point [ATSDR PHA at 14].

Even after 1972, Holcomb Boulevard intermittently received water from Hadnot Point, with TCE concentrations ranging from 38 ppb to 1,148 ppb. These concentrations exceeded CREG limits of 0.43 ppb by factors ranging from over 80 to more than 2,500.

G. RISK ASSESSMENTS

1. Risks based on CREG limits underrepresent actual cancer risk

The Cancer Risk Evaluation Guide (CREG) limits are established to achieve a "target risk level" of 1 x 10^{-6}, equivalent to a theoretical risk of one additional cancer case per million exposed individuals. These limits are intended to be conservative, focus on public health by minimizing the potential for cancer cases resulting from chemical exposure. However, CREG limits have notable limitations. Regulatory assessments, including those used to establish CREG levels, are not designed to estimate individual cancer risk; their primary focus is on identifying population-level hazards.

A limitation is that CREG levels are not cancer-specific. They define the general risk of cancer within a population without distinguishing between cancer types, such as leukemia or NHL. This stems from their regulatory purpose—agencies are tasked with identifying and mitigating unacceptable risks without the need to classify risks by cancer type. Whether a contaminant increases the likelihood of breast cancer or lung cancer is irrelevant to the decision to remediate the site; the focus is on addressing the hazard to public health as a whole. This approach avoids unnecessary delays for cleanup efforts.

Another limitation is that CREG levels are not designed to assess individual risk. The process of regulatory risk assessment is distinct from determining causation. While both rely on similar toxicological and epidemiological data, the goals are different. CREG levels seek to identify environmental conditions that warrant intervention, not to evaluate the likelihood of cancer causation for any particular person. This distinction is important when considering the limitations of dose-response models used in regulatory settings.

For example, cancer dose-response models do not account for inter-individual variability. Factors such as genetics, developmental stage, dietary habits, and behavior influence the way a person responds to chemical exposure. [Li L. Front Sustain. 2021;2:648138]. Because CREG levels are derived based on population medians, they may underestimate risks to individuals who are more vulnerable to toxic effects. Studies have documented these limitations, highlighting the potential for CREG levels to understate risk in sensitive individuals. [Varshavsky JR. Environ Health. 2023;21:133].

Despite these limitations, CREG levels remain effective for identifying hazards that necessitate intervention. Once a risk greater than 1 x 10^{-6} is demonstrated, site remediation is justified, regardless of whether the true risk is 1 x 10^{-6}, 1 x 10^{-4}, or even 1 in 10. The purpose of CREG limits is to highlight unacceptable risks, not to differentiate different degrees of high risk.

2. Theoretical risks are grounded in conservative assumptions

It is also important to understand that CREG limits are based on theoretical risks derived from animal studies rather than observed cancer rates in humans.[2] Dose-response curves in animal studies may not accurately reflect human physiology, and interspecies variation is well-documented. For example, the lethal dose of dioxin in guinea pigs is 0.1 micrograms per kilogram of body weight, while in hamsters, it is over 10,000 times greater. [EFSA Journal. 2018;16:5333]. This variability illustrates the challenges of translating animal study findings into human risk assessments.

Ethical constraints prevent exposing humans to carcinogens like TCE and PCE in controlled experiments, so scientists rely on animal data to extrapolate human risk. This process involves assumptions about dose-response relationships and cross-species equivalencies. [NTP 15th Report on Carcinogens Monographs on TCE and PCE, 2015].

Further, uncertainty increases at lower doses, where direct measurements are often unavailable. Scientists must make assumptions about how chemicals behave at these levels, leading to significant uncertainty that can span several orders of magnitude. [Slob W. Risk Analysis. 2014;34:1401-22].

3. Human epidemiology provides superior evidence

CREG limits should not be relied upon when there are better data available - for example, from human epidemiology dealing with the actual exposure scenario at issue.

Although CREG limits can provide an explanation for identifying environmental hazards, human epidemiological data are highly valuable for assessing cancer risk and identifying the levels of the toxins at issue that are known to cause bladder cancer. Epidemiological studies evaluate real-world exposures and outcomes, providing critical insights into the actual risk posed by contaminants and the actual levels of the contaminants that caused specific cancers. Unlike CREG levels, these studies sometimes can account for the combined effects of multiple chemicals and the synergistic interactions between them. [Vandenberg LN. Environ Health. 2022;21:121].

For instance, research specific to Camp Lejeune has consistently demonstrated elevated risks for cancers such as bladder cancer among those exposed to contaminated water. This real-world data

[2] For TCE, the cancer-slope was calculated in part based on a human occupational study by Charbotel [Charbotel B. Ann Occup Hyg 2006;50:777-87]. But as with the animal studies, the researchers in that study did not actually measure risk at lower levels of exposure. That is why the authors of that study stated that "further epidemiological studies are necessary to analyze the effect of lower levels of exposure."

highlights the limitations of CREG levels, which calculate risks for individual chemicals in isolation, often underestimating the cumulative risk from multiple exposures. The human epidemiology data, especially that taken directly from Camp Lejeuene is more accurate and provides a better analysis of the levels that are hazardous to humans generally and that cause bladder cancer.

4. The limited relevant data from risk assessment in this case supports the conclusion that the toxins at Camp Lejeune are hazardous to human generally and can cause bladder cancer

Rosendfeld *et. al* wrote an article in 2024 relating to the water at Camp Lejeune that, among other things, utilized a risk assessment analysis [PE. Water Air Soil Pollut 2024;235:124]. They calculated exposure scenarios using the same slope factors that are used to set the CREG levels. Rosenfeld and his co-authors calculated increased risks of between 1 and 75 in one million. This may seem to a layperson to be insignificant, however, the authors concluded that these results constituted a serious risk to people present at Camp Lejeune. The authors stated, "it can be reasonably concluded from the results and discussion that Camp Lejeune had significant enough water contamination to threaten the health of Marines living and working on the base." [Rosenfeld 2023 at 13]. They went on to state "bladder cancer" (among other diseases) poses "a high risk to individuals who spent time on the base, especially during the years of greatest contamination in the late 1970s and 1980s."

This is just one example of the CREG limit of 1×10^{-6} being interpreted by scientists as hazardous to humans generally during the use of risk assessments. Though a 1×10^{-6} risk may seem small, the numbers are not a precise estimate of the actual risk, as described above.

The 2017 ATSDR PHA also performed a risk assessment analysis and similarly concluded that the drinking water from Camp Lejeune posed an increased risk of cancer. [ATSDR PHA, 2017]. Specifically, ATSDR found that using "a 3-year exposure duration, the estimated upper-bound cancer risk exceeds the USEPA's Superfund target cancer-risk range (1 excess case for every 10,000 exposed persons to 1 excess case for every 1,000,000 exposed) during the years 1964–1985." Specifically, ATSDR found that:

- "Children living on-base from the early-1970s to the mid-1980s had an estimated, upper-bound cancer risk up to about 45 excess cases of cancer for every 10,000 exposed persons.
- Workers from the mid-1960s to the early-1980s had an estimated, upper-bound cancer risk of about three excess cases of cancer for every 10,000 exposed persons.
- Marines-in-training from the early-1970s to the early-1980s had an estimated, upper-bound cancer risk of about four excess cases of cancer for every 10,000 exposed persons.
- Other adults living on-base from the late-1970s to the early-1980s had an estimated, upper-bound cancer risk of about one excess case of cancer for every 10,000 exposed individuals."

Again, while these risk estimates may seem to a lay person to be low, understanding their purpose

and known flaws, these results are indicative of an increased risk for cancer and provide some support that the water at Camp Lejeune existed at levels that are hazardous to humans generally and are known to cause bladder cancer.

Finally, while CREG limits suggest a theoretical risk of 1×10^{-6}, the contaminant concentrations at Camp Lejeune vastly exceeded these levels. As detailed above, TCE and PCE concentrations at the base were often several orders of magnitude higher than the CREG limits. For example, the highest TCE concentration at Hadnot Point reached 1,400 ppb—more than 3,000 times the CREG limit for TCE. This provides additional support for the fact that the levels of toxins in the water at Camp Lejeune were hazardous to humans and were known to cause bladder cancer.

VII. ROUTES OF EXPOSURE TO THESE CHEMICALS

The topic of routes of exposure for the relevant identified chemicals naturally relates to the issue of the sources and concentrations of the subject chemicals in the potable water at the base during the statutorily delimited pertinent time period (1950s-1980s). With regard to background of the chemicals and data on their concentrations in the water, I have considered the work of the ATSDR for general background, however I do 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, and I defer to others with appropriate areas of expertise. With regard to historical factual background regarding the base during the time period at issue, I have in addition to ATSDR publications reviewed and considered the expert report of Dr. Kyle Longley prepared for this case. His report compiles information regarding historical facts of life and work at Camp Lejeune. I have not sought to independently verify Dr. Longley's report, however, I note that if the facts cited by Dr. Longley's report are accurate, they identify a variety of discrete VOC exposure settings at Camp Lejeune through the routes of ingestion, inhalation, and dermal exposure which are of potential significance to the present matter.

A. IN GENERAL

When evaluating the health effects of chemicals, it is important to understand how the chemicals enter and are distributed throughout the body. It is also important to understand how the body metabolizes and excretes the parent chemicals and their metabolites.

Chemicals such as PCE, TCE, benzene, and vinyl chloride are VOCs. People are exposed to VOCs in water by three major routes: inhalation, ingestion, and via dermal contact.

A number of studies have looked at the relative importance of those several routes. For example, over 25 years ago, Weisel and Jo determined estimates of internal doses of TCE due to showering [Weisel CP. and Jo WK. Environ Health Perspect 1996;104:48-51]. They concluded that inhalation and dermal exposure resulted in an internal dose of TCE comparable to the dose ingested in 2 liters of water. More recently, Gordon et al. investigated the contribution of household water use to internal doses of chloroform and other trihalomethanes [Gordon SM. Environ Health Perspect 2006;114:514-21]. They found that showering and bathing resulted in

the highest blood and exhaled-breath concentrations of chloroform with both inhalation and dermal absorption being important routes of exposure.

Demonstrating the importance of water temperature, Giardino and Andelman found that the volatilization of TCE during showering was most dependent on the temperature of water [Giardino NJ and Andelman JB. J Expo Anal Environ Epidemiol 1996;6:413-23]. Adding insight to the role that all three forms of exposure play in contributing to the internal dose of TCE, Haddad et al. used assessed different home exposure scenarios and concluded that ingestion contributed less than 50% of the total absorbed dose of TCE [Haddad S. J Toxicol Environ Health A 2006;69:2095-136]. Thus, absorption from the lungs, and the gastrointestinal tract, as well as from intact and broken skin dermal contact, must be taken into account when determining the internal dose that results from use of water contaminated with VOCs.

Whatever the route of exposure to a chemical, ultimately the portion of the chemical that enters the body from the lungs, gastrointestinal tract, or skin (sometimes termed the internal dose) is the portion that exerts biological effects. Pharmacokinetics (or toxicokinetics) and physiologically based toxicokinetic ("PBTK") models are important in addressing uncertainties inherently present in health risk assessments of the water contaminants at Camp Lejeune. Toxicokinetics can be defined as the absorption, distribution, metabolism, and elimination of chemicals. The kinetic processes determine how much of an external dose is absorbed into the blood, reaches systemic circulation; binds to proteins or other sites; enters specific organs; is biotransformed (if relevant) to toxicologically active and inactive forms; interacts with target molecules, cells, and tissues; and is eliminated from the target tissue and the body [Bruckner JV. Toxic effects of solvents and vapors. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 9th Ed]. One or more of those processes can vary widely from one route of exposure to another, from high to low doses, from one species to another, and from one individual to another. Furthermore, as discussed below, in a multi-chemical setting, chemicals mix. "Our knowledge of the toxicity of solvent mixtures is rudimentary relative to the toxicology of individual solvents. While the assumption is frequently made that the toxic effects of solvents are additive, the chemicals may also interact synergistically or antagonistically." [Bruckner JV. Toxic effects of solvents and vapors. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 9th Ed., Chapter 24 (Toxic Effects of Solvents and Vapors), p. 2 of 157].

Various scientific studies published regarding the relevant chemicals such as PCE and TCE have assessed exposure scenarios that involved potable water use and therefore implicitly the potable water exposure routes (ingestion, inhalation of vapor, and dermal). These have included studies reflecting comparable levels of VOC concentrations. See, e.g., Cohn P. Environ Health Perspect. 1994 Jun;102(6-7):556-61, at 557, which was a study of TCE and PCE drinking water contamination and leukemia and non-Hodgkin's lymphoma incidence in a 75-town area. "The highest assigned TCE level was 67 ppb, the highest assigned PCE level was 14 ppb…. The population-weighted concentrations of TCE and PCE in the highest categories were 23.4 ppb and 7.7 ppb, respectively. Four of the six municipalities in the highest TCE category were also in the highest PCE stratum. The population-weighted concentrations of TCE and PCE in the highest strata of the 48 municipalities added for this expanded study are 8.7 and 10.5 in 2 and 4 added

towns, respectively."). Also see Fagliano J. Drinking Water Contamination and the Incidence of Leukemia: An Ecologic Study. Am J Public Health 1990;80:1209-12. That study examined the relation between the incidence of leukemias and the occurrence of VOC contamination (TCE and related solvents) of drinking water supplies within a study area. The study described the data including the mean total VOC values assigned to each town or group of towns for the analysis. TCE, PCE, TCA, and dichloroethylenes (DCE) comprised nearly all of the non-THM VOCs involved. Based on inspection of the average values for each town, three categories of total VOCs were set: 1) 37 to 72 ppb, 2) 5 to 12 ppb, and 3) down to less than 1 ppb. Among other things the authors reported that "[t]he sum concentration of all non-THM VOCs was a statistically significant predictor of total leukemia incidence, adjusted for age." Id. at p. 1211.

As another example of a study involving VOCs in drinking water, see Aschengrau A. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health 1993;48:284-92, evaluating an exposure scenario involving PCE that leached from pipe liners into the public water supply. The abstract relates in part: "A population-based case-control study was used to evaluate the relationship between cases of bladder cancer (n = 61), kidney cancer (n = 35), and leukemia (n = 34) and exposure to tetrachloroethylene from public drinking water. Subjects were exposed to tetrachloroethylene when it leached from the plastic lining of drinking water distribution pipes. Relative delivered dose of tetrachloroethylene was estimated, using an algorithm that accounted for (1) residential history and duration, (2) whether lined pipe served the neighborhood, (3) distribution system flow characteristics, and (4) pipe age and dimensions. Whether or not latency was considered, an elevated relative risk of leukemia was observed among ever exposed subjects (adjusted OR = 1.96, 95% CI = 0.71-5.37, with latency; adjusted OR = 2.13, 95% CI = 0.88-5.19, without latency) that increased further among subjects whose exposure level was over the 90th percentile (adjusted OR = 5.84, 95% CI = 1.37-24.91, with latency; adjusted OR = 8.33, 95% CI = 1.53-45.29, without latency). When latency was ignored, there was also an increased relative risk of bladder cancer among subjects whose exposure level was over the 90th percentile (adjusted OR = 4.03, 95% CI = 0.65-25.10)." See id. A later publication regarding the same site described that "[t]ypical levels [of PCE slowly leaching from vinyl pipe liners] in affected towns ranged from 1,600 to 7,750 µg/L in low-flow locations, and from 1.5 to 80 µg/L in medium- and high-flow locations." [Aschengrau A. Environ Health Perspect, 2003 Feb;111(2):167-73 at 167.]

B. ABSORPTION VIA INGESTION

1. TCE

The evidence for oral ingestion absorption of TCE from water contamination is well-documented. Studies have shown that TCE is absorbed through the gastrointestinal tract when ingested. With regard to animal studies, Liu *et al.* demonstrated that TCE exhibits linear kinetics in rats over a dosage range of 0.1 to 5.0 mg/kg, with bioavailability ranging from 12.5% to 16.4%. [Liu Y. Drug Metab Dispo: Biol Fate Chem. 2009;37:1994-8]. This indicates that a significant portion of ingested TCE from water is absorbed into the bloodstream.

In volunteer studies in humans, Weisel and Jo found that ingestion of TCE from tap water leads to its complete metabolism before entering the bloodstream, suggesting that the absorbed dose is metabolized primarily in the liver. [Weisel CP and Jo WK. Environ Health Perspect. 1996;104:48-51] This presystemic metabolism reduces the amount of TCE reaching systemic circulation, but does not negate the fact that absorption occurs. Furthermore, as discussed in the mechanism of toxicity section of this report, TCE and the other halogenated hydrocarbons undergo metabolism to more toxic chemicals that damage DNA and cause cancer. [See Bruckner JV. Toxic effects of solvents and vapors. In Casarett and Doull's Toxicology: The Basic Science of Poisons, 9th Ed., at Chapter 24 (Toxic Effects of Solvents and Vapors), p. 25 of 157, stating that "[t]he adverse effects of TCE … are generally believed to be associated with TCE's metabolites."]. Publications since Weisel and Jo 1996 provide further insight on the mechanism of TCE absorption via ingestion. [*E.g.*, Lash LH, Fisher JW, Lipscomb JC, Parker JC. Metabolism of trichloroethylene. Environ Health Perspect. 2000 May;108 Suppl 2(Suppl 2):177-200. doi: 10.1289/ehp.00108s2177. PMID: 10807551; PMCID: PMC1637769.]

Additionally, Mortuza *et al.* reported that TCE exhibits nonlinear toxicokinetics with a disproportionate increase in area under the curve and a decrease in clearance with increasing doses, in rats further supporting the absorption and systemic distribution of TCE following oral ingestion. [Mortuza T. Toxicol Appl Pharmacol 2018;360:185-92].

2. PCE

Studies of controlled dosing of PCE in humans are lacking. In one case report, PCE was detected in blood at a concentration of 21.5 μg/mL approximately 1 hour after ingestion by a 6-year-old boy who had ingested between 12 to 16 g of PCE, demonstrating that PCE is absorbed following oral exposure in humans [Koppel C. Clin Toxicol 1985;23:103-15]. The evidence for oral ingestion absorption of PCE from water contamination is also supported by several studies. In a rat study by Frantz and Watanabe, they found after drinking-water administration, the elimination kinetics of PCE were not substantially different from the disposition resulting from inhalation [Frantz SW and Watanabe PG. Toxicol Appl Pharmacol 1983;69:66-72]. Pegg et al. also found that absorption of inhaled or oral PCE were essentially identical in rats [Pegg DG. Toxicol Appl Pharmacol 1979;51:465-74]. Similarly, PCE is nearly completely absorbed in dogs given a single dose by gavage [Dallas CE. Environ Res 1994;67:54-67].

In addition, a study by Wittlingerová *et al.* provides evidence of PCE contamination in surface water and its subsequent bioaccumulation in fish, indicating that PCE is indeed absorbed by organisms in contaminated water environments. [Wittlingerová Z. Environ Sci Poll Res Int 2016;23:5676-92].

The US EPA in 2012 completed a comprehensive toxicological review of PCE, which included an assessment of its toxicokinetics and metabolism. This review indicated that PCE is absorbed through the gastrointestinal tract when ingested, leading to systemic exposure. [Guyton KZ. Environ Health Perspect 2014;122:325-34].

3. Benzene

The evidence for oral absorption of benzene from water contamination is supported by several studies. In 1996, Beavers *et al.* assessed household exposure from gasoline-contaminated drinking water and found that ingestion of contaminated water contributed significantly to the total benzene dose, although inhalation during activities such as showering also played a major role. [Beavers JD. J Occup Environ Med 1996;38:35-8].

Santos et al. conducted a risk assessment following a gasoline station fuel leak and found that the population exposed to benzene-contaminated water had a significant intake of benzene through ingestion, with estimated benzene intake from water and food reaching up to 0.0091 µg/kg /day. [Santos M dos A. Rev Saúde Pública 2013;47(2):335-44]. The facts reflected that "the community was exposed to benzene from water consumption for 195 days and from water dermal contact and water vapor inhalation for 315 days. The mean concentration of benzene in the water estimated by the model during the oral exposure period (range of 5.1 to 235.5 µg/) was 72.6 µg/L (95%CI 40.9;104.2)."

See also generally Harrison R, Delgado Saborit JM, Dor F, et al. Benzene. In: WHO Guidelines for Indoor Air Quality: Selected Pollutants. Geneva: World Health Organization; 2010 ("Absorption of benzene is also rapid via the oral and dermal routes. Rats absorb and rapidly metabolize oral doses of benzene up to approximately 50 mg/kg.").

4. Vinyl chloride

The evidence for absorption of vinyl chloride after oral ingestion from water contamination is primarily derived from animal studies. Research indicates that vinyl chloride is absorbed and metabolized following oral administration. For instance, Green and Hathway demonstrated that after oral administration of C^{14} vinyl chloride to rats, the compound is primarily eliminated via the pulmonary route, with both unchanged vinyl chloride and its metabolites being excreted through the lungs and kidneys. This study also showed that the biotransformation of vinyl chloride involves several metabolic pathways, leading to the formation of various metabolites, including S-(2-chloroethyl) cysteine and N-acetyl-S-(2-chloroethyl) cysteine. [Green T and Hathway DE. Chem-Bio Interact 1975;11:545-62].

Additionally, Watanabe and Gehring found that the disposition of vinyl chloride in the body is dose-dependent, with higher doses saturating metabolic or detoxifying pathways, which could correlate with its oncogenic potential. [Watanabe PG and Gehring PJ. Environ Health Perspect 1976;17:145-52] This suggests that vinyl chloride is absorbed and metabolized in a manner that is influenced by the dose ingested.

See also generally World Health Organization 2004. Vinyl Chloride in Drinking-water. WHO/SDE/WSH/03.04/119, at 4 ("Animal studies show absorption of more than 95% after oral exposure.").

C. ABSORPTION VIA INHALATION

1. TCE

Weisel and Jo's research highlighted that individuals are exposed to volatile compounds like TCE from tap water not only through ingestion but also via inhalation and dermal absorption during activities such as showering. Their study found that inhalation exposure during showering can significantly increase the body burden of TCE, indicating that inhalation is a critical route of exposure from contaminated water. [Weisel CP and Jo WK. Environ Health Perspect 1996;104:48-51]. The investigators concluded that "[t]he internal dose derived from inhalation can be calculated from the air concentration, breathing rate, duration of the shower, and adsorption efficiency across the lung barrier." Furthermore, Weisel and Jo found that "approximately equivalent amounts of volatile contaminants from water can enter the body by three different exposure routes, inhalation, dermal absorption, and ingestion, for typical daily activities of drinking and bathing. However, the exposure route affects the rates of metabolism and therefore the compound's potential toxicity. The ingested VOCs were metabolized during the first pass through the liver, thus the parent compound was not measurable in the exhaled breath and would not be present in the bloodstream. However, chloroform and trichloroethene concentrations were measurable in the breath after inhalation and dermal exposure, indicating dispersion throughout the body."

Furthermore, Liu *et al.* assessed the health risks associated with different exposure pathways of volatile chlorinated hydrocarbons, including TCE, in contaminated drinking groundwater. They found that inhalation during showering posed a higher risk compared to oral ingestion, underscoring the importance of inhalational exposure in the overall risk assessment. [Liu W. Environ Pollut 2009;255:113339].

See also ATSDR Public Health Statement for Trichloroethylene (TCE), CAS#: 79-01-6 ("When trichloroethylene is found in water, it can enter your body when you drink or touch the water or when you breathe in steam from the water. Most of the trichloroethylene that you breathe in or drink will move from your stomach or lungs into your bloodstream.").

2. PCE

The evidence for inhalational absorption of PCE from water contamination is supported by several studies that demonstrate the presence of PCE in indoor air and exhaled breath following exposure to contaminated water sources.

Garnier *et al.* described the case of a boy who died in a room in which the curtains had been dry cleaned with PCE. He was asymptomatic when the door and windows were opened (thus providing ventilation), but when the door and windows were closed and he was put to bed for a nap, he died due to PCE exposure. On post-mortem examination he was found to have PCE in his blood at a concentration of 66 µ/mL [Garnier R. Clin Toxicol 1996;34:191-7].

One study conducted in Martinsville, Indiana, found that PCE was detected in all exhaled breath samples from residents living in areas with groundwater contamination, as well as in tap water

samples from their homes. This indicates that PCE can volatilize from contaminated water into indoor air, leading to inhalational exposure. [Liu S. Environ Pollut 2022;297:118756]

Another study measured chlorinated hydrocarbons, including PCE, in indoor air and exhaled air samples from individuals exposed to soil contamination. The study found significant levels of PCE in both indoor air and exhaled breath, demonstrating that PCE can intrude into indoor environments from contaminated sources and be absorbed through inhalation. [Scheepers PTJ. Sci Total Environ 2019;653:223-230].

3. Benzene

The evidence for inhalational absorption of benzene from water contamination is well-documented in the literature. Because benzene is also a volatile organic compound, it can be released into the air from contaminated water, particularly during activities that increase water agitation and temperature, such as showering or bathing.

A study by Beavers *et al.* assessed household exposure to benzene from gasoline-contaminated drinking water and found that inhalation exposure during showering contributed significantly to the total benzene dose. The estimated inhaled doses of benzene were similar to the ingested doses, with over half of the inhaled dose associated with shower activities. [Beavers JD. J Occup Environ Med 1996;38:35-8].

Similarly, Santos *et al.* conducted a risk assessment following a gasoline station fuel leak and found that benzene levels in water vapor during showering reached significant concentrations, posing a potential health risk. The study highlighted that inhalation during showering was a critical route of exposure, contributing to the overall benzene intake. [Santos M dos A. Rev Saúde Pública 2013;47(2):335-44].

4. Vinyl chloride

Pleil and Lindstrom demonstrated that vinyl chloride can be absorbed through inhalation during activities such as showering with contaminated water. They used the “single breath canister” technique to measure volatile organic compounds in exhaled breath, showing that vinyl chloride is detectable in breath samples post-exposure, indicating absorption through the respiratory route. [Pleil JD and Lindstrom AB. ClinChem 1997;43:723-30].

Additionally, studies on the pharmacokinetics of vinyl chloride in animal models, such as those by Buchter *et al.* and Hefner *et al.*, provide further evidence of rapid absorption and metabolism of vinyl chloride following inhalation. These studies showed that vinyl chloride equilibrates quickly and is extensively metabolized, supporting that inhalation is a significant route of exposure. [Buchter A. Toxicol Lett 1980;6:33-36; Hefner RE. Environ Health Perspect1975;11:85-95].

D. ABSORPTION VIA DERMAL EXPOSURE.

1. TCE

For 60 years the measurement of skin absorption of organic solvents such as TCE has been determined experimentally via their rates of decay in alveolar air [Stewart RD and Dodd HC. Am Industr Hyg Assoc J 1964;25:439-46]. However, it is unclear whether breath concentrations alone are a reliable measure of skin absorption. One reason for that is that significant differences in pharmacokinetics of chemicals can occur depending on the method of absorption. [Dollery CT. Ann NY Acad Sci 1971;179:108-14].

The evidence for dermal absorption of TCE from water contamination is supported by several studies. [Poet TS. Toxicol Sci 2000;56:61-72]. Poet *et al.* demonstrated that TCE can be absorbed through the skin in both rats and humans, with human skin showing a lower permeability coefficient (K(P) compared to rat skin. Specifically, the K(P) for TCE in a water matrix was 0.015 cm/h in humans, indicating that dermal absorption is a significant route of exposure. Nakai *et al.* also measured the permeability coefficient of TCE through human skin *in vitro*, finding a value of 0.12 cm/h, which supports the opinion that TCE can penetrate human skin from aqueous solutions. [Nakai JS. J Toxicol Environ Health 1999;58:157-70]

Weisel and Jo further corroborated these findings by showing that dermal absorption, along with inhalation, contributes to the total body burden of TCE from tap water exposure. [Weisel CP, Jo WK. Environmental Health Perspectives. 1996;104(1):48-51].

2. PCE

The evidence for dermal absorption of PCE from water contamination is supported by several studies. Nakai *et al.* also demonstrated that the permeability coefficient of PCE through human skin is 0.018 cm/h [Nakai JS. J Toxicol Environ Health 1999;58:157-70]. Dermal absorption of PCE occurs with exposure to the vapor form as well as the liquid form. When volunteers' forearms and hands were exposed to tetrachloroethylene vapor at a concentration of 6.68 mmol/L for 20 minutes, the absorption rate of PCE was 0.054 cm/h (3 times greater than the estimate of Nakai *et al.*), with a peak exhaled air concentration occurring 45 minutes after exposure began [Kezic S. Int Arch Occup Environ Health. 2000;73:415-22].

Citing a study by Bogen, the ATSDR has written that "a 70-kg human with a surface area of 18,000 cm^2, 80% immersed, would take up the [PCE] in 1L of water (of the total amount of water in which the person was immersed) in 20 minutes" [ATSDR Toxicological Profile for Tetrachloroethylene, 1997]. Studies such as these conclusively demonstrate that dermal absorption of PCE does occur and relevant and clinically important rates.

Hake and Stewart reviewed human exposure to PCE and noted that skin absorption can add to the overall exposure burden, particularly in occupational settings where both inhalation and dermal contact occur. [Hake CL and Stewart RD. Environ Health Perspect. 1977;21:231-8]. The authors stated, "Though absorption through the skin is usually not of as great consequence as through the

lungs, it should not be overlooked as a contributory factor to the [PCE] body burden. . . ."

3. Benzene.

The evidence for dermal absorption of benzene from water contamination is supported by several studies that have investigated the percutaneous absorption of benzene in various settings. Williams *et al.* reviewed and analyzed data from multiple studies and found that the steady-state dermal flux for benzene-saturated aqueous solutions ranges from 0.2 to 0.4 mg/(cm²·h). [Williams PR. Crit Rev Toxicol 2011;41:111-42] This indicates that benzene can penetrate the skin at measurable rates when present in water.

Modjtahedi and Maibach conducted an *in vivo* study on human subjects and found that the total absorption of benzene through the skin was nominal, with forearm exposure showing an average total absorption of 0.07±0.04% and palmar exposure an average total absorption of 0.13±0.04% of the applied dose. [Modjtahedi BS and Maibach HI. Food Chem Toxicol. 2008;46:1171-4]. These findings suggest that while dermal absorption of benzene from water is possible, the overall absorption rates are relatively low under controlled conditions.

4. Vinyl chloride.

Data regarding the dermal absorption of vinyl chloride are mixed. According to a review on the systemic absorption of chemical vapors, the dermal contribution ratio (DCR) for vinyl chloride is approximately 0.0002, indicating that the amount absorbed through the skin relative to total intake (skin and inhalation) is low. This suggests that vinyl chloride is primarily absorbed through inhalation rather than through the skin. The low DCR is largely explained by the chemical properties of vinyl chloride, such as its octanol:water partition coefficient and vapor pressure. [Rauma M. Adv Drug Deliv Rev 2013;65:306-14].

VIII. LITERATURE REVIEW

A. OCCUPATIONAL STUDIES

The occupational literature convincingly demonstrates that TCE, PCE, and benzene can cause bladder cancer. Although some of the exposure assessments in the occupational literature were qualitative, that is not unusual. "Many of the causal associations between chemicals and human disease have been developed from epidemiological studies relating a workplace chemical to an increased risk of the specific disease in cohorts of workers, often with only a qualitative assessment of exposure." [Ref Manual at 657]. And although some of the occupational studies involved exposure to TCE and PCE at high concentrations, "the levels of TCE in the Hadnot Point distribution system were sufficiently high to result in exposures comparable to those that may occur in some occupational settings." [Bove 2014a at 11]. A Marine stationed at Camp Lejeune could have a possible *daily* exposure "as high as 3.6 mg/day." [Bove 2014a at 11]. That kind of exposure is comparable to the occupational literature.

A few of the occupational studies are worth discussing in more detail, as they provide insight into

the levels of TCE/PCE exposure that can cause bladder cancer.

A 2014 meta-analysis of occupational PCE exposure by Vlaanderen *et al.* found a summary relative risk of 1.47 (95% CI 1.16-1.85). [Vlaanderen J. Environ Health Perspect 2014;122:661-6]. Among the case-control studies evaluated by Vlaanderen (all of which adjusted for smoking), the summary RR was 1.50 (95% CI 0.80-2.84) which was similar to the summary relative risk found among the cohort studies of 1.46 (95% CI 1.14-1.87), which indicates that the cohort studies were unlikely to be biased by confounding by smoking.

Another cohort study of dry cleaners by Lynge *et al.* found relative risks of 1.44 (95% CI 1.07-1.93) and 1.69 (95% CI 1.18-2.43) for all Nordic countries and analyses restricted to Denmark and Norway, respectively. [Lynge E. Environ Health Perspect 2006;114:213-9].

Additionally, a National Institute for Occupational Safety and Health dry cleaning worker study by Calvert *et al.* found an increase in death due to bladder cancer with a standardized mortality ration of 2.59 (95% CI 1.24-4.76) for workers in who's shops primarily used PCE [Calvert GM. Occup Environ Med 2011;68:709-16].

B. WATER-CONTAMINATION STUDIES

The studies discussed above demonstrate that TCE, benzene, and PCE are capable of causing bladder cancer. While the concentrations of these chemicals in the studies were often higher than those at Camp Lejeune, this does not imply that lower exposure levels are not capable of causing bladder cancer. These studies focused on higher levels of exposure and, by design, did not address the impact of lower levels. What they do confirm with a high degree of certainty is that the elevated exposure levels observed in occupational studies are sufficient to cause bladder cancer.

However, the occupational studies represent only one part of the body of research on TCE, PCE, benzene, and bladder cancer. Beyond the occupational literature, literature has shown that these chemicals can also cause bladder cancer at lower levels of exposure. Specifically, studies on other water contamination incidents in the U.S. have provided evidence that chemical exposures similar to those at Camp Lejeune are sufficient to increase the risk of bladder cancer, as detailed below.

As noted earlier, randomized controlled trials are not feasible in this context due to ethical considerations, and incidents like the contamination at Camp Lejeune are rare. Most public water supplies in the U.S. do not contain significant levels of these chemicals, either individually or in combination. [Bexfield LM. Sci Tot Environ 2022;827:154313]. As a result, there are fewer human epidemiological studies addressing the effects of these chemicals at lower exposure levels compared to the occupational literature. Nonetheless, existing studies have shown an increased risk of bladder cancer among individuals exposed to lower levels of TCE, PCE, and benzene.

1. Aschengrau et al., 1993, Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts

Aschengrau *et al.* reviewed the cancer risk experienced by a cohort of individuals exposed to PCE

on Cape Cod, Massachusetts, after "it was discovered that PCE was leaching into drinking water." [Aschengrau A. Arch Environ Health: Intern J 1993;48:284-92 at 284]. Following this discovery, the Massachusetts Department of Health observed "elevations in cancer mortality" in the affected areas. [Aschengrau at 285]. In the towns with the highest PCE concentrations, levels ranged from 1.5-80 µg per liter at medium and high-use sites to 1,600-7,750 µg per liter at low-use sites. These levels are comparable to the concentrations found at Camp Lejeune's Hadnot Point and Tarawa Terrace systems.

Researchers in this study also constructed a measure of Relative Delivered Dose (RDD) to model the total amount of PCE consumed by individuals on Cape Cod. The 90th percentile for cumulative exposure was 27.1- 44.1 milligrams. For comparison these levels are in the same range of cumulative exposures experienced by individuals at Camp Lejeune. For example, if a Marine at Camp Lejeune consumed water from Tarawa Terrace in 1984, when PCE concentrations were about 150 ppb (equivalent to 0.150 mg/liter), and drank 4.29 liters of water per day (calculated based on drinking 6 liters per day for three days a week and 3 liters per day for the other four days), they would have a cumulative exposure of 44 mg over 68 days. See [ATSDR 2017 at 3] ("A marine in training at Camp Lejeune consumes an estimated 6 liters of water per day for three days per week and 3 liters per day the rest of the week (ATSDR 2016). Under warm weather conditions, a Marine may consume between 1 and 2 quarts of water per hour and shower twice a day."). This exposure would place the Marine in the 90th percentile of cumulative exposure in the Aschengrau study, meaning they would have received more PCE than 90% of participants in that study.

A Marine present at Camp Lejeune during lower rates of PCE concentration still could have received comparable levels. For example, if the Marine's exposure was from Hadnot Point rather than Tarawa Terrace, where PCE concentrations reached a lower maximum of around 39 ppb (39 µg per liter, equivalent to 0.039 milligrams per liter), and the Marine consumed 4.29 liters per day would accumulate a total of 44 mg of PCE in approximately 263 days. A duration of 263 days to reach 44 mg of PCE is easily within the mean time at Camp Lejeune for Marines of 18 months. A number of other scenarios, where a Marine stationed on Camp Lejeune would have a cumulative PCE exposure equivalent to those seen at the 90th percentile on Cape Cod, are possible.

The Aschengrau authors then went on to define the risk of bladder cancer (and other cancers) for the Cape Cod cohort. For people who were exposed to any amount of PCE, the relative risk of bladder cancer was measured at 1.55 (95% CI 0.74-3.01), suggesting a 55% increased risk. Adjusting relative risk to control for confounders "only slightly" changed the relative risk for bladder cancer to 1.39 (95% CI 0.67-2.91). Further indication of causation is the effect an individual's bathing habits had on their relative risk. With confounders controlled, the relative risk of bladder cancer among subjects who took mostly baths increased to 1.99 (95% CI 0.40-10.01).

Although these results were not statistically significant, that is unsurprising given that the study had a small sample size and was therefore underpowered. And in any event, "a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association." [2017 ATSDR at 8].

For people exposed to high amounts of PCE - above the 90th percentile, equivalent to a cumulative exposure of 27-44 milligrams - the measured risk was even higher. High PCE exposure produced a risk ratio of 6.04 (95% CI 1.32-21.84), suggesting a 504% increased risk of bladder cancer. The authors noted that bladder cancer's increased risk "appeared to be dose related," – that is, as the cumulative amount of PCE increased, so did the risk of bladder cancer. The study authors ultimately concluded that they had "found evidence for an association between PCE-contaminated public drinking water" and "bladder cancer." [Aschengrau 1993 at 291]

This study provides evidence that people exposed to comparable levels of PCE as Camp Lejeune are at an increased risk of bladder cancer.

C. EVIDENCE FROM CAMP LEJEUNE studies CONFIRMS THAT THESE CHEMICALS CAUSE BLADDER CANCER AT DETECTED CONCENTRATIONS

Extensive research has already shown that TCE, benzene, and PCE are capable of causing bladder cancer, with the risks evident at levels comparable to those found in Camp Lejeune's water. What sets Camp Lejeune apart is the rare availability of human epidemiological studies directly examining individuals exposed to these chemicals at the site. These studies of most importance when looking at effects of these exposures, confirming a link between the contaminated water and an increased risk of bladder cancer among those exposed.

One key part of the Camp Lejeune studies is that it moves beyond theoretical cancer risk calculations. Cancer slope models, often derived from animal studies and used to predict risks like 1-in-a-million, significantly understate the real-world risk observed in Camp Lejeune's exposed population. The epidemiological findings provide a much clearer picture of the actual health outcomes, showing risks far higher than those theoretical models suggest. This direct evidence gives us a superior understanding of the true impact of the contamination.

The Camp Lejeune studies also give insight into the cumulative effects of multiple chemical exposures. Many Camp Lejeune residents were exposed to TCE, PCE, benzene, and vinyl chloride simultaneously. Studies and scientific literature suggest that these exposures are not merely additive but could interact synergistically, creating a combined risk that is greater than the sum of individual risks. [Rosenfeld 2024 at 14] This interaction amplifies the potential harm, reinforcing the need to consider the full scope of the exposure rather than isolating each chemical's effect.

Moreover, the Camp Lejeune data provides conclusive evidence that the chemical concentrations present were sufficient to induce bladder cancer. The unique epidemiological focus on Camp Lejeune offers rare and strong data that support and strengthens the existing body of evidence, leaving little doubt about the harm posed to humans by these contaminants at the levels detected in the water at Camp Lejeune.

It is also important to note that the Camp Lejeune epidemiology may itself understate the increased risk to bladder cancer specifically, and there are at least two reasons to believe the effect of exposure is even greater than portrayed in the below literature. First, bladder cancer has a relatively

higher survival rate compared to other cancers the epidemiology looked at. Therefore, the studies that look at mortality do not fully capture the group of people whose bladder cancer was caused by water exposure at Camp Lejeune. Second, bladder cancer occurs primarily in older adults. Consequently, earlier epidemiology likely failed to identify individuals who would later be diagnosed with bladder cancer as a result of their exposure at Camp Lejeune, thereby understating the effect of exposure. ATSDR recognized these shortcomings in its assessment: "Bladder cancer occurs mainly in older people and has a 5-year survival percentage of over 77%. Because the Camp Lejeune cohorts were relatively young at the end of follow-up, few deaths due to bladder cancer occurred." [ATSDR 2017 at 95]. This helps explain the lack of causal relationship seen in the 2014 Bove studies.

It should be pointed out that urothelial carcinoma of the renal pelvis is a type of kidney cancer, and that epidemiologic studies generally include urothelial carcinoma of the renal pelvis under cancer of the kidney. But renal pelvis urothelial carcinoma is cytologically more similar to bladder cancer. However, as this cancer type has typically been included under kidney cancer in epidemiologic studies, I have likewise considered it under the umbrella of kidney cancer, which is covered in a separate report. Lastly, all four of the chemicals at issue here cause urothelial carcinoma of the renal pelvis.

1. ATSDR 2018 Study: Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune

The 2018 ATSDR morbidity study [ATSDR. Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune, April 2018] was conducted by the Agency for Toxic Substances and Disease Registry and surveyed over 200,000 Marines stationed at Camp Lejeune between 1972-1985, along with a comparator group of 50,000 Marines stationed at Camp Pendleton during that same period. The survey also included more than 8,000 civilians who worked at Camp Lejeune and a comparator of 7,000 civilians who worked at Camp Pendleton. The study aimed "to evaluate whether exposure to the contaminated drinking water at Camp Lejeune was associated with medically confirmed specific diseases of interest."

The results showed that Marines at Camp Lejeune had an odds ratio of developing bladder cancer of 1.64 (95% CI 1.02-2.64), indicating a 64% increased risk compared to the Marines at Camp Pendleton. While civilians at Camp LeJeune had a odds ratio of ≤1.0, the odds ratios for civilians with high exposure was 1.8 compared to civilians at Camp Pendleton and other civilians at Camp Lejeune with lower amounts of exposure. (95% CI 0.50-6.53 for Camp Pendleton; 95% CI 0.47-6.77 for the internal analysis). These findings provide compelling evidence that exposure to the water at Camp Lejeune - and therefore, the exposure to the chemicals present in the water during 1972-1985 - is sufficient to cause bladder cancer.

The study also analyzed bladder cancer risk based on specific degree of chemical exposure,

comparing Marines at Camp Pendleton with those at Camp Lejeune who had varying degrees of exposure to the specific chemicals water.

Using water distribution models and residential locations and periods of residence at Camp Lejeune, the authors calculated cumulative and average residential exposure to each contaminant. Marines at Camp Lejeune with any/low exposure to TCE (defined less than 110 ppb-months) had an the odds ratio for bladder cancer was 1.28 (95% CI .0.76-2.15) - a 28% increased risk versus their peers at Camp Pendleton. The odds ratio for Marines at Camp Lejeune with medium exposure to TCE (defined as between 110 and 11,030 ppb-months) increased for bladder cancer to 1.68 (95% CI 1.00-2.82), a 68% increased risk versus their peers at Camp Pendleton. These results suggest not only that 110 ppb-months of exposure to TCE is enough to increase the risk of bladder cancer, but that risks increase at doses below 110 ppb-month.[3]

Marines with low exposure to PCE (defined less than 36 ppb-months) had an odds ratio of bladder cancer of 1.33 (95% CI 0.80-2.24) - a 33% increased risk versus their peers at Camp Pendleton. Medium exposure to PCE (defined as between 36 and 711 ppb-months), showed an odds ratio of bladder cancer of 1.30 (95% CI 0.76-2.23). For Marines with high exposure to PCE (more than 711 ppb-months), the odds ratio increased to 2.07 (95% CI 1.12-3.82). These results suggest that both doses between 36 and 711 ppb-months of exposure to PCE and doses less than 36 ppb-month are enough to increase the risk of bladder cancer.

As a final comparative set, study authors looked at Camp Lejeune personnel who were exposed to higher amounts of TCE and PCE and personnel stationed at Camp Lejeune who were exposed to lower amounts. Marines exposed to 110 ppb-months of TCE had an increased risk of bladder cancer of 1.34 (95% CI 0.98-1.85). These results show 110 ppb-months of TCE exposure is sufficient to increase the bladder cancer risk.

Marines who were exposed to 36 ppb-months of PCE had an odds ratio 0.99 (95% CI 0.69-1.40) as compared to marines exposed to lower amounts. Significantly, that shows that Marines with any exposure had the same risk of contracting bladder cancer as those who were exposed to 36 ppb-months; importantly, both groups had a higher risk of bladder cancer than the Marines at Camp Pendleton. These results indicate that very low levels of PCE exposure are enough to increase the risk of bladder cancer.

2. Bove 2024b Study: *Cancer Incidence Among Individuals Exposed to Contaminated Drinking Water at Camp Lejeune*

The 2024 cancer incidence study [Bove FJ. Environ Health Perspect 2024;132:107008-1 through 15]] compared cancer rates at Camp Lejeune to the similar cohort at Camp Pendleton. The study then examined cancer incidence of cancer among these individuals between 1996 and 2017 in order to determine whether being stationed or employed at Camp Lejeune increased the risk of cancer incidence. Camp Pendleton, which housed a similar population but "was not known to have

[3] These results also of course suggest that 11,030 ppb-months is also enough. Again, these are not thresholds but simply levels that have been shown to increase the risk in the human epidemiology.

contaminated drinking water," was viewed as an ideal comparator to base the experimental design upon. The two populations of Marines/Navy personnel and civilians theoretically are identical in all material respects except for the exposure to hazardous amounts of the chemicals described above experienced by the Camp Lejeune cohort.[4]

In addition to the overall comparison of cancer rates between Camp Lejeune and Camp Pendleton, the study also analyzed cancer risk in relation to the total exposure to the chemicals, using "duration of assignment" (for the Marines/Navy) and "duration of employment" (for the civilians) "as a surrogate for overall cumulative exposure." For Marines, "low duration" was defined as 1-6 quarters, "medium duration" was defined as 7-10 quarters, and "high duration" was defined as more than 10 quarters on base. For civilian workers, "low/medium duration" was defined as 1-21 quarters on base, and "high duration" was defined as >21 quarters on base.

Again, results found that individuals stationed at Camp Lejeune had a higher incidence of bladder cancer. Overall, Marines and Navy personnel showed a relative risk of 1.09 (95% CI 0.95-1.24) and civilians showed a relative risk of 1.10 (95% CI 0.91-1.50). These findings suggest exposure to the water at Camp Lejeune, particularly during the years 1975-1985, increases the risk of bladder cancer.

3. Rosenfeld 2024 Study: *Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955 to 1987*

The 2024 study by Rosenfeld *et al*. employed cancer-slope and other health-assessment methodologies to evaluate the cancer risk for Marines stationed at Camp Lejeune between 1953 and 1987. The authors determined that even a single month of working on the base during the period from 1980 to 1984 could result in a cancer risk exceeding the 1 in a million de minimis threshold. [Rosenfeld 2024 at 10]. For Marines with six months on the base, the risk increased up to sixfold compared to the one-month exposure scenario. [Rosenfeld 2024 at 11].

The cancer-slope calculations have limitations acknowledged above in this report. Cancer-slope calculations are used to estimate potential risk rather than to establish causation. The theoretical risks calculated for Camp Lejeune exceeded the de minimis threshold, indicating potential harm. Human epidemiological studies show that the actual risks observed in exposed populations are higher than those estimated by these models. This suggests that the contamination at Camp Lejeune had measurable impacts beyond those predicted by theoretical assessments.

The findings from Rosenfeld *et al*. are consistent with epidemiological data showing that even short-term exposure to contaminated water at Camp Lejeune carried notable risks.

[4] Camp Pendleton was chosen in these studies as a comparison based on the assumption that the Camp Pendleton cohort was not exposed to these chemicals. But there is some suggestion in the literature that even the Marines and civilians at Camp Pendleton might have been exposed. If so, that does not undermine the signal being generated from these studies. To the contrary, if the Camp Pendleton cohort was also exposed, that suggests that the results comparing Camp Lejeune to Camp Pendleton would be biased toward the null, *i.e.*, it suggests that the risk ratios in these studies are *understated*, and that if a comparison had been made to a population of Marines that was truly unexposed, the risk ratios would have been even higher.

IX. OTHER RELEVANT CONSIDERATIONS

A. CARCINOGENIC LATENCY

The concept of latency is important when discussing adverse health effects, including cancer. In short, latency is the amount of time that elapses between an exposure to a carcinogen and the diagnosis of cancer. However, there are several confounding factors when assessing cancer latency because of exposure, especially as cancer risk increases over one's lifetime. A significant limitation to much of toxin-induced cancer research is the reliance on mortality from cancer rather than on the diagnosis. This concept is critically important when trying to determine the risk of cancer from a toxic exposure, because mortality studies will only detect the cancer if the person dies of that cancer. However, if someone dies *with* a cancer (rather than because of the cancer), then that person would not be counted as having developed cancer from the exposure, thus severely limiting the ability for mortality studies to detect an association between exposure and cancer. Furthermore, if a person has developed cancer due to an exposure, but their death certificate does not expressly list the cancer as the cause of death (*e.g.*: the person dies of a myocardial infarction or stroke which were unrelated to their cancer), then that patient would also not be counted as having died of their toxin-induced cancer. For these reasons, mortality studies are likely to underestimate this issue.

Important information about cancer latency comes from studies performed in Hiroshima and Nagasaki, Japan. The detonation of the atomic bombs provided a perfectly established exposure time to a known carcinogen (ionizing radiation). A number of study cohorts from Japan have been followed for nearly 80 years, providing information on the increased risk of cancers, as well as latency, and the effect of age of exposure to a carcinogen and cancer development. Preston *et al.* examined members of the Life Span Study of Hiroshima and Nagasaki survivors through 1998. They found a 17% decrease in the risk of cancer for every decade of age at the time of the bombing [Preston DL. Rad Res 2007;168:1-64]. Preston has followed-up that study with another examining excess risk of cancers in people exposed *in utero* or in childhood to ionizing radiation [Preston DL. J Natl Cancer Inst 2008;100:428-36]. They found excess absolute rates of cancer increased markedly with attained age among those exposed in early childhood but exhibited little change in the *in utero* group. At age 50, the estimated excess absolute rates per 10,000 person-years per Sievert (a measure of radiation exposure) were 6.8 for those exposed *in utero,* and 56 for those exposed as young children. This data is important and informative for the people exposed to the carcinogens from water at Camp Lejeune. Firstly, the risk of adverse effects (at least carcinogenicity) is greatest for *in utero* and childhood exposures. Secondly, there is a significant latency to the development of cancer after exposure. Thus, ongoing psychological stress and the need for medical monitoring needs to be considered.

B. ADDITIVE AND SYNERGISTIC EFFECTS OF SOLVENTS AND TOXINS

Adding to the complexity of the Camp Lejeune fact set and the potential for toxicity was that the Camp Lejeune water was contaminated with at least four different chlorinated hydrocarbons--PCE, TCE, DCE, vinyl chloride – as well as by benzene. The ATSDR data reflects that when

contemporaneous samples of the potable water were taken and analyzed in the early 1980s, all five chemicals were detected including at levels above today's maximum contaminant levels (MCLs).[5] Several of the chemicals were detected during the same overlapping time periods at Hadnot Point. Further, numerous individuals residing at Tarawa Terrace would have gone about their days at Hadnot Point before going home in the evening, thereby receiving exposures to mixtures of the chemicals already mixed together in the Hadnot Point water treatment system and the Tarawa Terrace water system. It is reasonably inferable that all or most individual exposures were exposed to more than one of the relevant chemicals in the drinking water.

Further, it should be noted that these chemicals are molecules. The structural similarity between the 4 chlorinated VOCs at issue herein is striking. The differences between the molecular series proceeding from PCE to vinyl chloride may be conceptualized roughly as starting with a structure with four chlorine atoms (thus the "tetra" (Latin for four) in tetrachloroethylene), then deleting one chlorine atom from the structure (leading to TCE, "tri"), then deleting one more chlorine atom (reducing to DCE, "di"), and then deleting one more (leaving vinyl chloride).

As one may intuit from the above rough conceptualization, under the right environmental conditions, PCE may degrade into TCE, and so forth, over time. Thus, in groundwater conditions, PCE initially undergoes a classical decomposition as a result of dehalogenated reduction to TCE and the Cl^- ion under aerobic conditions around Eh +100 (+50) to 0 mV. While maintaining the double bond between the carbon atoms, TCE decays under slightly reducing conditions of around Eh -50 to -100 mV to dichloroethene (DCE) and Cl^-. [Pierri D. Environ Adv 2021;5:100090]. The fact that PCE may degrade into TCE over time supports the contention that ultimately Camp Lejeune residents exposed to one of the chemicals were likely to have also been exposed to others (highlighting the question of additive effect).

PCE and TCE also upon ingestion can generate common metabolites, which can themselves by mutagenic, genotoxic, or carcinogenic.[6] "Trichloroethylene (TCE) and tetrachloroethylene (PCE) are structurally similar chemicals" and "are structurally similar chlorinated olefins." [Luo YS. Toxicol 2018;409:33-43]. An analysis of the comparative toxicokinetics of TCE and PCE reveals that upon absorption, TCE and PCE are metabolized through oxidative and glutathione conjugation pathways. [Cichocki JA,. J Pharmacol Exp Ther 2016;359:110123]. Initial oxidation occurs on the double bond by cytochrome P450s (CYPs) to generate an epoxide, which can be further metabolized. Trichloroacetic acid (TCA) is a major oxidative metabolite of both TCE and PCE, and is a common urinary biomarker of exposure. [Forkert PG. Drug Metab Dispos 2003;31:306-11]. As of 2014, TCA was classified by the EPA as a possible human carcinogen based on evidence

[5] *See* Figure 4 in Maslia ML. Water 2016;8:449. *See also id.* at Table 2, listing selected "measured and reconstructed (simulated) concentrations of tetrachloroethylene (PCE), trichloroethylene (TCE), *trans*-1,2-dichloroethylene (1,2-tDCE), vinyl chloride, and benzene at the Hadnot Point water treatment plant."

[6] A genotoxin is a chemical or agent that can damage DNA or chromosomes in a cell, potentially causing mutations that lead to cancer or birth defects. A genotoxic agent can bind directly to DNA or indirectly damage it by affecting enzymes involved in DNA replication. Genotoxicity is a more general term than mutagenicity. A mutagen is a mutation-causing agent, such as a chemical, which results in an increased rate of mutations in an organism's genetic code. All mutagens are also genotoxins. A genotoxic carcinogen or mutagenic carcinogen can include a chemical that can damage the genetic material of a cell in a manner that can contribute to lead to cancer.

of carcinogenicity in experimental animals. [IARC Monograph 106, 2014]. As of 2012, TCA was considered to be a confirmed carcinogen in experimental animals.

In addition to metabolization producing TCA, TCE is also metabolized into the oxidative metabolite, trichloroethanol (TCOH), which is a TCE-specific metabolite that is formed through oxidation of TCE to chloral hydrate (CH), while PCE oxidation occurs through trichloroacetyl chloride.[7] TCOH and related chemicals have been studied for their carcinogenic potential.[8]

There are other common metabolites as between PCE and TCE. For instance, upon absorption, both TCE and PCE can enzymatically conjugate with glutathione to form dichloro- or trichloro-glutathione conjugates (DCVG or TCVG).[9] These can be further metabolized via hepatic or renal gamma-glutamyl transferase and di-peptidase to form corresponding cysteine conjugates, DCVC or TCVC, which are then n-acetylated via N-acetyltransferase to generate NAcDCVC or NAcTCVC, respectively.[10] In addition, both NAcDCVC and NAcTCVC can be deacetylated via acylase to yield DCVC or TCVC, respectively. Apart from N-acetylation, DCVC and TCVC can be further bio-activated via cysteine conjugate β lyase to generate reactive thioketenes, or flavin-containing monooxygenase to form corresponding sulfoxides.[11]

In short, the science reflects that unsurprisingly structurally similar chemicals – e.g., PCE and TCE – once absorbed into the body by ingestion, inhalation or dermal exposure routes, can be broken down or metabolized into other substances. Some of these metabolites or breakdown products are common as between the parent chemicals.

When exposure to more than one chemical occurs (as, here, to e.g. PCE and TCE), there is the potential for 3 major types of interactions: either a) the toxic effects are additive (e.g.: 1 + 1 = 2); or b), the effects are less than truly additive (e.g.: 2 + 2 = 3);[12] or c), the effects are synergistic (e.g.: 1 + 1 = 3). Any significant deviation from additivity would be classified as synergy or antagonism. Synergy can be defined as a combination effect that is greater than the additive effect expected. Synergy can also be called superadditivity.

Documented evidence of various particular additive or synergistic effects of two different exposures, contaminants or stressors, include, in one study, evidence of how obesity was observed to increase the risk of arsenic-associated lung and bladder cancer by over 10-fold in individuals with elevated arsenic exposure compared to non-obese individuals. [Steinmaus C. Environ Res.

[7] Luo 2018, citing Chiu WA. Toxicol Sci 20078;95:23-36.
[8] *See* Robert Kapp, Encyclopedia of Toxicology (Second Edition), 2005, discussing 2,2,2-Trichloroethanol and noting that acyl chlorides and free radicals that are formed from both 1,1,1-trichloroethane and 1,1,2-trichloroethane are believed to bind nucleic acids and proteins causing various cytoxic, mutagenic, and carcinogenic effects.
[9] Luo 2018, citing Lash LH. Environ Health Perspect 2000;108:177-200.
[10] *Id.*
[11] Luo 2018, citing Lash LH. Mutat Res Rev Mutat Res 2014;762:22-36.
[12] For example, assume that drinking only chemical X for a year causes a 2% chance of cancer, and drinking only chemical Y for a year causes a 3% chance of cancer; and because of some interaction between them, if one drinks both X and Y for a year, the cancer risk rises but only to 4%. Under "normal" additive conditions, using the simple math the additive effect should have been 5% instead.

2015;142:594–601]. Studies indicate that arsenic's carcinogenicity is synergistically higher in obese individuals, smokers, and those with concurrent occupational exposures. [Steinmaus 2015; Ferreccio C. Epidemiol 2013;24:898–905]. As another specific example of apparent synergistic carcinogenic effect, a 2000 publication described a supra-additive genotoxicity of a combination of γ-irradiation and ethyl methanesulfonate in exposed mouse cells.[13]

One of the first synergistic interactions described between environmental pollutants was with a mixture of asbestos and cigarette smoke, which promotes the development of lung cancer.[14] The science of additive and synergistic interactions between multiple chemical contaminants such as, e.g., the PCE, TCE, DCE, vinyl chloride, and benzene series here, is evolving. However, 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.

Concepts of additive effect of multiple exposures to different carcinogens and environmental contaminants over time is related to the hypothesis of carcinogenesis as additive across various exposures and stressors. In this regard, cumulative risk assessment has been defined as the assessment of "combined risks from aggregate exposures to multiple agents or stressors, where agents or stressors may include chemical and nonchemical stressors." U.S. EPA. Framework for cumulative risk assessment. U.S Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment; Washington, DC: 2003.

X. BRADFORD HILL ANALYSIS

A. TCE

I generally followed the weight of the evidence approach to investigating and analyzing the data on TCE exposure and adverse health effects in the Camp Lejeune cohort, and the development of bladder cancer specifically. However, I have also evaluated bladder cancer effects and water through consideration of the Bradford Hill "criteria." Published as nine viewpoints in 1965, the Bradford Hill criteria are often used to determine if observed epidemiologic associations are causal. Those nine principles are: strength of association; consistency; specificity; temporality; biological gradient; plausibility; coherence; experiment; and analogy. Applying these criteria to

[13] *See* Stopper H. Mutagenesis 2000;15:235-8 (from the Abstract: "While testing for genotoxicity is usually performed on single chemicals, exposure of humans always comprises a number of genotoxic agents. The investigation of potentially synergistic effects of combinations therefore is an important issue in toxicology. Combinations of 511 keV γ-radiation with the chemical alkylating agent ethyl methane-sulfonate were investigated in the in vitro micronucleus test in mouse lymphoma L5178Y cells. With combinations in the low dose linear effect range for the individual agents (0.25–2 Gy and 0.8–3.2 mM, respectively), supra-additivity by 34–86% was seen. The synergism was more pronounced at the higher dose levels. Supra-additivity was confirmed in experiments using cytochalasin B and analyzing binucleate cells only, to control for putative effects on the cell cycle. Statistical significance was shown by a 2-factor analysis of variance with interaction….").

[14] *See* Alejandro F. GeoHealth 2022;6 (so stating).

the association between the chemicals at Camp Lejeune and leukemia, there is substantial evidence supporting causality.

Strength of Association: Strength of association is demonstrated by statistical significance. That is, an odds ratio for the occurrence of an adverse health effect in those exposed to TCE of greater than 1.1. 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. Studies of Camp Lejeune personnel as well studies of occupational exposure and other environmental pollution events reliably demonstrate risks of greater than 1.1 for exposure to TCE and bladder cancer. Evidence for the strength of association criterion comes from the Hadkhale study [Hadkhale 2017]. They found the hazard ratio for TCE exposure was 1.23 (95% CI 1.12-1.40) when comparing high exposure levels to no exposure. The authors summarized that this finding indicates that "the estimated exposure to trichloroethylene was significantly associated with an increased risk of bladder cancer."

Consistency: The Bradford Hill term of consistency refers to the concept that studies done in different populations or that studies of different designs yield similar results. This criterion is also met in that studies consistently demonstrate bladder cancer after exposure to TCE. For example, both Hadkhale *et al.* [Hadkhale K. Inter J Cancer. 2017;140:1736-46] and the ATSDR 2018 morbidity study demonstrated an increased risk of bladder cancer with TCE exposure.

Specificity: Specificity in Bradford Hill's time meant that an exposure causes a single disease without any other likely explanation other than the exposure under consideration. However, we now know that a particular exposure may cause more than one disease state. For instance, it is known that the water contaminants from Camp Lejeune are known to cause several cancers and other adverse health effects. Therefore, the specificity criterion is difficult to meet with TCE.

Temporality: Temporality is the easiest of the Bradford Hill criteria to understand, and the one criterion that must be met. Simply put, the exposure must precede the development of the disease. This criterion is also met in the issue at hand with regards to the Camp Lejeune water contamination.

Biological Gradient: The concept of a biological gradient is that a dose-response exists. That is, that the greater a dose (i.e., exposure), the more likely a response (i.e., presence of disease). However, we now know that complex dose-response relationships can occur (e.g.: hormesis) and that dose-response relationships are not all (or necessarily) linear. Data from Camp Lejeune and from occupational exposures and other environmental contamination sites do provide evidence of a positive dose-response for exposure to TCE and the occurrence of bladder cancer.

Plausibility: Biologic plausibility refers to the concept that a relationship between an exposure and an adverse health outcome can be attributed to causation based on existing biomedical and epidemiological knowledge. In the above report, some of the research into the mechanism of action and varied outcomes after TCE exposure was detailed. Specifically, TCE is metabolized into toxic

intermediates that can cause DNA damage and chromosomal aberrations, which are mechanisms known to contribute to carcinogenesis. There have been several epidemiological studies performed for TCE. Given this abundant evidence, it is my opinion that the biologic plausibility standard has been met with regards to TCE exposure and bladder cancer.

Coherence: The Bradford Hill criterion of coherence is very similar to biological plausibility. That is, that "the cause-and-effect interpretation of the data should not seriously conflict with the generally known facts of the natural history and biology of the disease" [Bradford Hill 1965]. TCE is a known carcinogens. There are mechanistic, animal, and human studies evaluating the effect of the chemicals on gene expression and chromosomal abnormalities, and the occurrence of bladder cancer. It is my opinion that the criterion of coherence has also been met.

Experimental Evidence: Bradford Hill also identified experimentation as a criterion to evaluate with regards to causation. Put simply, conduct experiments whereby you either purposely expose individuals to a toxin (such as TCE), or you eliminate such an exposure and determine the effect on adverse health outcome occurrence. Clearly one cannot ethically subject individuals for any significant length of time to TCE by any method of exposure. However, there are decades of epidemiologic research which demonstrate that TCE causes cancer, and specifically that TCE causes bladder cancer. Therefore, it is my opinion that the experimentation criterion has also been met.

Analogy: With analogy, Bradford Hill meant to say that when there is strong evidence of an exposure-disease dyad, one should be more inclined to accept causation with a similar exposure and/or disease. There is ample scientific evidence of chlorinated solvents (including TCE) causing various cancers, with TCE specifically causing bladder cancer. With the wide range and varied adverse effects (including carcinogenesis) of the chlorinated solvents including TCE, it is my opinion that the analogy criterion has also been met.

When the body of research on TCE exposure is considered in light of the Bradford Hill criteria, I am able to opine that exposure to TCE causes bladder cancer. However, it is also important to note that the Bradford Hill criteria were not intended to be rigid guidelines or a checklist that must be completed in order to determine causation. Rather, they are suggested guidelines to consider when determining causation.

B. PCE

I generally followed the weight of the evidence approach to investigating and analyzing the data on PCE exposure and adverse health effects in the Camp Lejeune cohort, and the development of bladder cancer specifically. However, I have also evaluated bladder cancer effects of PCE exposure with consideration of the Bradford Hill "criteria."

Strength of Association: Strength of association is demonstrated by statistical significance. That is, an odds ratio for the occurrence of an adverse health effect in those exposed to the contaminated Camp Lejeune water of greater than 1.1. 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. Studies of Camp Lejeune personnel as well studies of occupational exposure and other environmental pollution events reliably demonstrate risks of greater than 1.1 for exposure to PCE and bladder cancer. For example, Hadkhale *et al.* reported hazard ratios of 1.12 (95% CI 1.02-1.23) for perchloroethylene at medium exposure levels [Hadkhale K. Inter J Cancer. 2017;140:1736-46].

Consistency: The Bradford Hill term of consistency refers to the concept that studies done in different populations or that studies of different designs yield similar results. This criterion is also met in that studies consistently demonstrate bladder cancer after exposure to PCE. For example, Hadkhale *et al.* found an increased risk of bladder cancer, and ATSDR " . . . conclude that there is sufficient evidence for causation for PCE and bladder cancer." [ATSDR Assessment of the Evidence for the Drinking Water, 2017 at 95].

Specificity: Specificity in Bradford Hill's time meant that an exposure causes a single disease without any other likely explanation other than the exposure under consideration. However, we now know that a particular exposure may cause more than one disease state. For instance, it is known that the water contaminants including PCE cause several cancers and other adverse health effects. Therefore, the specificity criterion is difficult to meet with regards to PCE at Camp Lejeune.

Temporality: Temporality is the easiest of the Bradford Hill criteria to understand, and the one criterion that must be met. Simply put, the exposure must precede the development of the disease. This criterion is also met in the issue at hand with regards to the Camp Lejeune water contamination.

Biological Gradient: The concept of a biological gradient is that a dose-response exists. That is, that the greater a dose (i.e., exposure), the more likely a response (i.e., presence of disease). However, we now know that complex dose-response relationships can occur (e.g.: hormesis) and that dose-response relationships are not all (or necessarily) linear. A population-based case-control study by Hadkhale *et al.* found an increased risk of bladder cancer associated with occupational exposure to PCE, with the highest excess risk observed at medium exposure levels. Additionally, a meta-analysis of dry-cleaning worker studies by Vlaanderen indicated an increased risk of bladder cancer among workers exposed to PCE, with a meta-relative risk (mRR) of 1.08 (95% CI 0.82-1.42) for PCE-exposed workers and 1.47 (95% CI 1.16-1.85) for dry cleaners (Vlaanderent 2014). This analysis suggests evidence for an exposure-response relationship, although the exposure assessment methods were relatively crude.

Plausibility: Biologic plausibility refers to the concept that a relationship between an exposure and an adverse health outcome can be attributed to causation based on existing biomedical and epidemiological knowledge. In the above report, some of the research into the mechanism of action and varied outcomes after PCE exposure were detailed. Specifically, PCE is metabolized into toxic intermediates that can cause DNA damage and chromosomal aberrations, which are mechanisms

known to contribute to carcinogensis. It is therefore my opinion that the biologic plausibility standard has been met with regards to exposure and bladder cancer.

Coherence: The Bradford Hill criterion of coherence is very similar to biological plausibility. That is, that "the cause-and-effect interpretation of the data should not seriously conflict with the generally known facts of the natural history and biology of the disease" [Bradford Hill 1965]. PCE is a known carcinogen. There are mechanistic, animal, and human studies evaluating the effect of PCE on gene expression and chromosomal abnormalities, and the occurrence of bladder cancer. It is my opinion that the criterion of coherence has also been met.

Experimental Evidence: Bradford Hill also identified experimentation as a criterion to evaluate with regards to causation. Put simply, conduct experiments whereby you either purposely expose individuals to a toxin (such as PCE), or you eliminate such an exposure and determine the effect on adverse health outcome occurrence. Clearly one cannot ethically subject individuals for any significant length of time to PCE by any method of exposure. However, there are decades of epidemiologic research which demonstrate that PCE causes cancer, and specifically that PCE causes bladder cancer. Therefore, it is my opinion that the experimentation criterion has also been met.

Analogy: With analogy, Bradford Hill meant to say that when there is strong evidence of an exposure-disease dyad, one should be more inclined to accept causation with a similar exposure and/or disease. There is ample scientific evidence of chlorinated and other solvents (including TCE, PCE, and benzene) causing various cancers, with TCE, PCE, and benzene specifically causing bladder cancer. With the wide range and varied adverse effects (including carcinogenesis) of the chlorinated and other solvents, it is my opinion that the analogy criterion has also been met.

When the body of research on PCE exposure is considered in light of the Bradford Hill criteria, I am able to opine that exposure to PCE causes bladder cancer. However, it is also important to note that the Bradford Hill criteria were not intended to be rigid guidelines or a checklist that must be completed in order to determine causation. Rather, they are suggested guidelines to consider when determining causation.

C. BENZENE

I generally followed the weight of the evidence approach to investigating and analyzing the data on benzene exposure and adverse health effects in the Camp Lejeune cohort, and the development of bladder cancer specifically. However, I have also evaluated bladder cancer effects and water through consideration of the Bradford Hill "criteria."

Strength of Association: Strength of association is demonstrated by statistical significance. That is, an odds ratio for the occurrence of an adverse health effect in those exposed to the contaminated Camp Lejeune water of greater than 1.01. 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 1.1 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. Studies of Camp Lejeune personnel as well studies of occupational exposure and other environmental pollution events reliably demonstrate risks of greater than 1.1 for exposure to benzene and bladder cancer. For example, Hadkhale *et al.* reported hazard ratios (HRs) of 1.16 (95% CI 1.04-1.31) for benzene and [Hadkhale K. Inter J Cancer. 2017;140:1736-46].

Consistency: The Bradford Hill term of consistency refers to the concept that studies done in different populations or that studies of different designs yield similar results. This criterion is also met in that studies consistently demonstrate bladder cancer after exposure to benzene. For example, both Hadkhale *et al.* [Hadkhale K. Inter J Cancer. 2017;140:1736-46] and Shala *et al.* found increased risks of bladder cancer with benzene exposure, with Shala *et al.* reporting HRs of 1.89 (95% CI 1.14-3.13) for long-term benzene exposure [Shala NK. Br J Cancer 2023;129:838].

Specificity: Specificity in Bradford Hill's time meant that an exposure causes a single disease without any other likely explanation other than the exposure under consideration. However, we now know that a particular exposure may cause more than one disease state. For instance, it is known that benzene is known to cause several cancers and other adverse health effects. Therefore, the specificity criterion is difficult to meet with benzene.

Temporality: Temporality is the easiest of the Bradford Hill criteria to understand, and the one criterion that must be met. Simply put, the exposure must precede the development of the disease. This criterion is also met in the issue at hand with regards to the Camp Lejeune water contamination.

Biological Gradient: The concept of a biological gradient is that a dose-response exists. That is, that the greater a dose (i.e., exposure), the more likely a response (i.e., presence of disease). However, we now know that complex dose-response relationships can occur (e.g.: hormesis) and that dose-response relationships are not all (or necessarily) linear. Data from Camp Lejeune and from occupational exposures and other environmental contamination sites do provide evidence of a positive dose-response for exposure to benzene and the occurrence of bladder cancer. For example, Hadkhale (Hadkhale 2017) and Xie (Xie 2024) observed increased bladder cancer risks with higher exposure levels to benzene indicating a dose-response relationship.

Plausibility: Biologic plausibility refers to the concept that a relationship between an exposure and an adverse health outcome can be attributed to causation based on existing biomedical and epidemiological knowledge. In the above report, some of the research into the mechanism of action and varied outcomes after benzene exposure were detailed. Specifically, benzene metabolized into toxic intermediates that can cause DNA damage and chromosomal aberrations, which are mechanisms known to contribute to carcinogensis. There have been several epidemiological studies performed for the chemicals at issue here. Given this abundant evidence, it is my opinion that the biologic plausibility standard has been met with regards to benzene exposure and bladder cancer.

Coherence: The Bradford Hill criterion of coherence is very similar to biological plausibility. That is, that "the cause-and-effect interpretation of the data should not seriously conflict with the

generally known facts of the natural history and biology of the disease" [Bradford Hill 1965]. Benzene is a known carcinogen. There are mechanistic, animal, and human studies evaluating the effect of benzene on gene expression and chromosomal abnormalities, and the occurrence of bladder cancer. It is my opinion that the criterion of coherence has also been met.

Experimental Evidence: Bradford Hill also identified experimentation as a criterion to evaluate with regards to causation. Put simply, conduct experiments whereby you either purposely expose individuals to a toxin (such as benzene), or you eliminate such an exposure and determine the effect on adverse health outcome occurrence. Clearly one cannot ethically subject individuals for any significant length of time to these chemicals by any method of exposure. However, there are decades of epidemiologic research which demonstrate that benzene causes cancer, and specifically that benzene cause bladder cancer. Therefore, it is my opinion that the experimentation criterion has also been met.

Analogy: With analogy, Bradford Hill meant to say that when there is strong evidence of an exposure-disease dyad, one should be more inclined to accept causation with a similar exposure and/or disease. There is ample scientific evidence of solvents (including benzene) causing various cancers, with benzene specifically causing bladder cancer. With the wide range and varied adverse effects (including carcinogenesis) of solvents, it is my opinion that the analogy criterion has also been met.

When the body of research on benzene exposure is considered in light of the Bradford Hill criteria, I am able to opine that exposure to benzene causes bladder cancer. However, it is also important to note that the Bradford Hill criteria were not intended to be rigid guidelines or a checklist that must be completed in order to determine causation. Rather, they are suggested guidelines to consider when determining causation.

D. VINYL CHLORIDE

I generally followed the weight of the evidence approach to investigating and analyzing the data on vinyl chloride exposure and adverse health effects in the Camp Lejeune cohort, and the development of bladder cancer specifically. However, I have also evaluated bladder cancer effects and water through consideration of the Bradford Hill "criteria."

Strength of Association: Strength of association is demonstrated by statistical significance. That is, an odds ratio for the occurrence of an adverse health effect in those exposed to vinyl chloride of greater than 1.1. 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. A long-term mortality study of vinyl chloride workers by Mundt et al. found a standardized mortality ratio of 1.29 (95% CI 0.91-1.57) for bladder cancer. [Mundt KA. Occup Environ Med 2017;74:709–716]

Consistency: The Bradford Hill term of consistency refers to the concept that studies done in

different populations or that studies of different designs yield similar results. This criterion is also met in that studies consistently demonstrate bladder cancer after exposure to solvents. However, vinyl chloride in isolation has not consistently been shown to cause bladder cancer.

Specificity: Specificity in Bradford Hill's time meant that an exposure causes a single disease without any other likely explanation other than the exposure under consideration. However, we now know that a particular exposure may cause more than one disease state. For instance, it is known that vinyl chloride causes several cancers and other adverse health effects. Therefore, the specificity criterion is difficult to meet with the chemical contaminants at Camp Lejeune.

Temporality: Temporality is the easiest of the Bradford Hill criteria to understand, and the one criterion that must be met. Simply put, the exposure must precede the development of the disease. This criterion is also met in the issue at hand with regards to the Camp Lejeune water contamination.

Biological Gradient: The concept of a biological gradient is that a dose-response exists. That is, that the greater a dose (i.e., exposure), the more likely a response (i.e., presence of disease). However, we now know that complex dose-response relationships can occur (e.g.: hormesis) and that dose-response relationships are not all (or necessarily) linear. Data from Camp Lejeune and from occupational exposures and other environmental contamination sites do provide evidence of a positive dose-response for exposure to solvents and the occurrence of bladder cancer. For example, Hadkhale *et al.* [Hadkhale K. Inter J Cancer. 2017;140:1736-46] and Xie *et al.* [Xie S. J Exposure Sci Environ Epidemiol 224;34:546-53] observed increased bladder cancer risks with higher exposure to solvents, indicating a dose-response relationship.

Plausibility: Biologic plausibility refers to the concept that a relationship between an exposure and an adverse health outcome can be attributed to causation based on existing biomedical and epidemiological knowledge. In the above report, some of the research into the mechanism of action and varied outcomes after vinyl chloride exposures were detailed. Specifically, vinyl chloride metabolized into toxic intermediates that can cause DNA damage and chromosomal aberrations, which are mechanisms known to contribute to carcinogenesis. Given this evidence, it is my opinion that the biologic plausibility standard has been met with regards to exposure and bladder cancer.

Coherence: The Bradford Hill criterion of coherence is very similar to biological plausibility. That is, that "the cause-and-effect interpretation of the data should not seriously conflict with the generally known facts of the natural history and biology of the disease" [Bradford Hill 1965]. Vinyl chloride is a known carcinogen. There are mechanistic, animal, and human studies evaluating the effect of vinyl chloride on gene expression and chromosomal abnormalities, and the occurrence of bladder cancer. It is my opinion that the criterion of coherence has also been met.

Experimental Evidence: Bradford Hill also identified experimentation as a criterion to evaluate with regards to causation. Put simply, conduct experiments whereby you either purposely expose individuals to a toxin (such as vinyl chloride), or you eliminate such an exposure and determine the effect on adverse health outcome occurrence. Clearly one cannot ethically subject individuals for any significant length of time to vinyl chloride by any method of exposure. Direct experimental

evidence of vinyl chloride exposure and bladder cancer has not been met.

Analogy: With analogy, Bradford Hill meant to say that when there is strong evidence of an exposure-disease dyad, one should be more inclined to accept causation with a similar exposure and/or disease. There is ample scientific evidence of chlorinated and other solvents (including TCE, PCE, vinyl chloride, and benzene) causing various cancers, including bladder cancer. With the wide range and varied adverse effects (including carcinogenesis) of the chlorinated solvents, it is my opinion that the analogy criterion has also been met.

When the body of research on vinyl chloride is considered in light of the Bradford Hill criteria, I am able to opine that exposure to vinyl chloride causes bladder cancer. However, it is also important to note that the Bradford Hill criteria were not intended to be rigid guidelines or a checklist that must be completed in order to determine causation. Rather, they are suggested guidelines to consider when determining causation.

E. TVOC

I generally followed the weight of the evidence approach to investigating and analyzing the data on TVOC exposure and adverse health effects in the Camp Lejeune cohort, and the development of bladder cancer specifically. However, I have also evaluated bladder cancer effects and water through consideration of the Bradford Hill "criteria."

Strength of Association: Strength of association is demonstrated by statistical significance. That is, an odds ratio for the occurrence of an adverse health effect in those exposed to the contaminated Camp Lejeune water of greater than 1.1. 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. Occupational exposure to TVOCs has been linked to an increased risk of bladder cancer (Xie 2024 and Hadkhale 2017).

Consistency: The Bradford Hill term of consistency refers to the concept that studies done in different populations or that studies of different designs yield similar results. This criterion is also met in that studies consistently demonstrate bladder cancer after exposure to TVOC. For example, the Hadkhale *et al.* study was performed in Scandinavia while the Xie *et al.* study was conducted in New England.

Specificity: Specificity in Bradford Hill's time meant that an exposure causes a single disease without any other likely explanation other than the exposure under consideration. However, we now know that a particular exposure may cause more than one disease state. For instance, it is known that the water contaminants from Camp Lejeune are known to cause several cancers and other adverse health effects. Therefore, the specificity criterion is difficult to meet with the chemical contaminants at Camp Lejeune.

Temporality: Temporality is the easiest of the Bradford Hill criteria to understand, and the one

criterion that must be met. Simply put, the exposure must precede the development of the disease. This criterion is also met in the issue at hand with regards to the Camp Lejeune water contamination.

Biological Gradient: The concept of a biological gradient is that a dose-response exists. That is, that the greater a dose (i.e., exposure), the more likely a response (i.e., presence of disease). However, we now know that complex dose-response relationships can occur (e.g.: hormesis) and that dose-response relationships are not all (or necessarily) linear. Data from occupational exposures do provide evidence of a positive dose-response for exposure to TVOC and the occurrence of bladder cancer. For example, Hadkhale (Hadkhale 2017) and Xie (Xie 2024) observed increased bladder cancer risks with higher exposure to TVOCs, indicating a dose-response relationship.

Plausibility: Biologic plausibility refers to the concept that a relationship between an exposure and an adverse health outcome can be attributed to causation based on existing biomedical and epidemiological knowledge. In the above report, some of the research into the mechanism of action and varied outcomes after TCE, PCE, benzene, and vinyl chloride exposures were detailed. Specifically, the chemicals are metabolized into toxic intermediates that can cause DNA damage and chromosomal aberrations, which are mechanisms known to contribute to carcinogensis. There have been several epidemiological studies performed for the chemicals at issue here. Given this abundant evidence, it is my opinion that the biologic plausibility standard has been met with regards to exposure and bladder cancer.

Coherence: The Bradford Hill criterion of coherence is very similar to biological plausibility. That is, that "the cause-and-effect interpretation of the data should not seriously conflict with the generally known facts of the natural history and biology of the disease" [Bradford Hill 1965]. The water contaminants at Camp Lejeune are known or probable carcinogens. There are mechanistic, animal, and human studies evaluating the effect of the chemicals on gene expression and chromosomal abnormalities, and the occurrence of bladder cancer. It is my opinion that the criterion of coherence has also been met.

Experimental Evidence: Bradford Hill also identified experimentation as a criterion to evaluate with regards to causation. Put simply, conduct experiments whereby you either purposely expose individuals to a toxin (such as TCE, PCE, benzene, and vinyl chloride), or you eliminate such an exposure and determine the effect on adverse health outcome occurrence. Clearly one cannot ethically subject individuals for any significant length of time to these chemicals by any method of exposure. However, there are decades of epidemiologic research which demonstrate that the Camp Lejeune water contamination chemicals cause cancer, and specifically that they cause bladder cancer. Therefore, it is my opinion that the experimentation criterion has also been met.

Analogy: With analogy, Bradford Hill meant to say that when there is strong evidence of an exposure-disease dyad, one should be more inclined to accept causation with a similar exposure and/or disease. There is ample scientific evidence of chlorinated and other solvents (including TCE, PCE, benzene, and vinyl chloride) causing various cancers. With the wide range and varied

adverse effects (including carcinogenesis) of the chlorinated solvents, it is my opinion that the analogy criterion has also been met.

When the body of research on the combined chemicals from Camp Lejeune (as TVOC) is considered in light of the Bradford Hill criteria, I am able to opine that exposure to these chemicals causes bladder cancer.

XI. CONCLUSION

The water at Camp Lejeune was contaminated for decades with TCE, PCE, vinyl chloride, and benzene. It is my opinion that these water contaminants have been shown to cause adverse health effects, including bladder cancer, 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.

It is also my opinion that the levels of exposure to these chemicals at Camp Lejeune are hazardous to humans, and specifically as likely as not cause bladder cancer. Epidemiologic studies of occupational exposure to these chemicals, as well as environmental contamination by these chemicals, provide evidence that the level of exposure to these chemicals on Camp Lejeune were sufficient to cause bladder cancer.

Respectfully,

Steven B. Bird, MD

Appendix A

Nov 2024

Steven B. Bird, M.D.

PERSONAL INFORMATION

Address:	Department of Emergency Medicine University of Massachusetts Medical School 55 Lake Avenue North LA-167 Worcester, MA. 01655 USA
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Fax:	(508) 421-1490
E-mail:	steven.bird@umassmemorial.org

EDUCATION

M.D., *Alpha Omega Alpha* 1991 – 1995
Northwestern University
Chicago, Illinois

B.S. Biology, *cum laude* 1987 – 1991
Yale University
New Haven, Connecticut

POST-GRADUATE TRAINING

Fellow in Toxicology 2002 – 2004
University of Massachusetts Medical School
Worcester, MA

Chief Resident in Emergency Medicine 2001 – 2002
University of Massachusetts Medical School
Worcester, MA

Resident in Emergency Medicine 1999 – 2002
University of Massachusetts Medical School
Worcester, MA

US Naval Flight Surgeon 1996 – 1999
Marine Corps Air Station Futenma
Okinawa, Japan

Resident in Surgery 1995 – 1996
Naval Hospital San Diego
San Diego, CA

LICENSURE AND BOARD CERTIFICATION

American Board of Emergency Medicine, 2003 and 2013

American Board of Toxicology, 2004 and 2014

Massachusetts Physician License # 205932

ACADEMIC APPOINTMENTS

Professor of Emergency Medicine — 3/2016 - current
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Associate Professor of Emergency Medicine — 1/2010 – 3/2016
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Assistant Professor of Emergency Medicine — 9/2004 – 1/2010
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Instructor of Emergency Medicine — 8/2002 – 8/2004
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

DEPARTMENTAL, SCHOOL, and HOSPITAL APPOINTMENTS

Chief of Medical Toxicology — 3/2024 – current
UMassMemorial Health
Worcester, MA

IT Steering Council — 2/2020 – 11/2024
UMassMemorial Health
Worcester, MA

Space Allocation and Utilization Committee — 2/2020 – 2022
UMass Medical School & UMassMemorial Health
Worcester, MA

Clinician Experience Officer (CXO) — 9/2019 – 11/2024
UMassMemorial Health
Worcester, MA

Medical Center/Medical Group Leadership Team — 9/2019 – 11/2024
UMassMemorial Health
Worcester, MA

Joint Leadership Team — 9/2019 – 11/2024
UMass Medical School & UMassMemorial Health

Worcester, MA

Chair, Division Director of EMS Search Committee 3/2017 - 1/2018
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Comprehensive Stroke Center Director Search Comm. 8/2016 - 12/2016
University of Massachusetts Medical School
Worcester, MA

Clinician Health and Well-Being Committee Co-Chair 8/2015 – 11/2024
University of Massachusetts Medical School
Worcester, MA

Dept of Neurosurgery Chair Search Committee 9/2014 - 6/2016
University of Massachusetts Medical School
Worcester, MA

Dept of EM Clinical Quality Review Committee 7/2013 - current
UMassMemorial Health
Worcester, MA

Medical Staff President 7/2013 - 6/2015
UmassMemorial Health
Worcester, MA

Chief Medical Officer Search Committee 6/2013 - 9/2013
UMassMemorial Health
Worcester, MA

Vice Chair of Education 3/2012 - 9/2019
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Chair of Hospital Credentials Committee 7/2011 - 6/2013
UMassMemorial Health
Worcester, MA

Medical Staff President-Elect 7/2011 - 6/2013
UMassMemorial Health
Worcester, MA

Assistant Director of Clinical Operations 3/2011 - 11/2013
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

Program Director for Emergency Medicine Residency 3/2011 - 8/2019
University of Massachusetts Medical School
Worcester, MA

Medical Staff Executive Committee 6/2010 – 11/2024
UMassMemorial Medical Center
Worcester, MA

Attending Emergency Physician 7/2002 - current
University of Massachusetts Medical Center
Worcester, MA

Attending Emergency Physician 7/2002 - current
Marlborough Hospital
Marlborough, MA

Attending Emergency Physician 7/2002 - current
Clinton Hospital
Clinton, MA

MEMBERSHIPS AND SOCIETIES

Council of Residency Directors for Emergency Medicine 2011- 2019

American College of Medical Toxicology 2001 - current

Massachusetts College of Emergency Physicians 1999 - current

Society for Academic Emergency Medicine 1998 - current

American College of Emergency Physicians 1998 - current

HONORS AND AWARDS

Outstanding Contribution to Medical Toxicology Research 2021
American College of Medical Toxicology

National Leadership Award 2019
UMass Department of Emergency Medicine

Emergency Medicine Residency Teaching Award 2018
UMass Emergency Medicine Residency

Emergency Medicine Residency Teaching Award 2016
UMass Emergency Medicine Residency

Lean Yellow Belt 2015

Best Scientific Presentation 2014
American College of Medical Toxicology Annual Meeting

Team Award for Quality Care 2012
UMassMemorial Healthcare

Lean White Belt 2012

Best New Speaker Award 2012
American College of American Physicians Annual Meeting
Perfect audience evaluation score of 100%.

Young Investigator Award Society for Academic Emergency Medicine	2007
Best Resident Basic Science Presentation Society for Academic Emergency Medicine	2002
Excellence in Research Award New England Regional Research Directors	2002
Navy and Marine Corps Achievement Medal	1999
Alpha Omega Alpha	1994
Yale University Richter Fellow	1990

PROFESSIONAL ACTIVITIES

Departmental/Institutional

Division Chief of Medical Toxicology 3/2024 – current
UMassMemorial Health
Worcester, MA

- Responsible for executive direction and execution of 9-person Division of Medical Toxicology and its 4 fellows.

Claims Committee 4/2021 - current
UMassMemorial Health
Worcester, MA

- Member of the Claims Committee of our self-insured captive
- Review all claims and lawsuits brought against UMassMemorial Health and covered individuals
- Evaluate each claim and lawsuit and give recommendations to the Director of Risk Management and the CEO with regards to defense, settlement, or trial, as well as recommend financial limits on any settlement

Clinician Experience Officer (CXO) 9/2019 – 11/2024
UMassMemorial Health, Medical Group, and Medical School
Worcester, MA

- CXO for jointly funded position of the health system, group practice, and medical school. Responsible for all wellness and engagement activities for all physicians, advanced practice providers, residents, and fellows.
- Led efforts that saw our Press Ganey physician engagement at the University Campus climb from the 1st percentile to the 18th percentile.
- Reports directly to hospital president, Dean, and group practice president.
- Member of Medical Center/Medical Group Leadership Team as well as Joint Leadership Team (involving medical school).
- Successfully led to UMass joining the Stanford Physician Wellness Academic Consortium in June 2020.
- Created a cadre of wellness coaches to allow for free wellness coaching for all faculty, residents, and fellows.
- Jointly-led the Caring for the Caregiver efforts during COVID-19 pandemic.

Peer Support Program 6/2016 – 11/2024
UMassMemorial Health
Worcester, MA

- Creator, with the assistance of a competitive grant from risk management, of a peer support network at UMassMemorial Healthcare. The peer support network is a group of 25 physicians trained in providing assistance to physicians facing difficulties related to poor patient outcomes, litigation, and other stressors. The Peer Support Program receives a new referral roughly once every 2 weeks.

Clinician Health and Well-Being Committee 8/2015 – 11/2024
UMassMemorial Health
Worcester, MA

- Selected by System CMO to co-chair the Clinician Health and Well-Being Committee (CHWC). The mission of this committee is to proactively identify, counsel, and refer physicians before an adverse event occurs.

Wellness Committee Chair 4/2015 - current
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

- Created a wellness committee for our residency and department. Invited national speakers on the topic and facilitated a “Notes Day” (modeled on the process improvement structure of Pixar) to help identify local, institutional, and departmental factors associated with physician burnout. Instituted wellness initiatives within the residency, including a wellness and empathy curriculum.

Vice Chair of Education 3/2012 - 9/2019
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

- Responsible for all aspects of education within the Department of Emergency Medicine, including undergraduate, graduate, and allied health professional education. The Department has 40 residents in a PGY1-3 residency; 70+ faculty members; 911fellows; and UMass and visiting medical students.

- Oversaw the development and implementation of mandatory UMass medical student class “Emergency Clinical Problem Solving”. This class began in May, 2013, and is required for all 125 4th year medical students. Responsible for 4th-year medical student elective in Emergency Medicine. Direct report for 5 physicians and oversees staff of 4 administrative assistants.

President of the Medical Staff 7/2013 - 6/2015
UMassMemorial Health

- Served a two-year term as president of the medical staff. Responsible for review of all new and renewal applications to the medical staff. Coordinated with Chief Medical Officer all institution peer reviews, including the Chief Physician Officer, hospital general counsel, applicable department chairs, and the individual physician in question. As president of the medical staff I also presided over quarterly medical staff meetings, participated in Joint Commission preparation focus groups, and assisted the Chief Medical Officer and Group Practice President as needed.

Clinical Competency Committee 3/2012 – 7/2024
Emergency Medicine Residency

University of Massachusetts Medical School
Worcester, MA

- Responsible for determining the competency and promotion for 36 emergency medicine residents and coordinates decisions with the Graduate Medical Education office.

Chair, Medical Staff Credentialing Committee 7/2011 - 6/2013
UMassMemorial Health

- Served two years as Chair of the Medical Center's credentialing. Reviewed all new and renewal applications to the medical staff. Coordinated with Chief Medical Officer and Department Chairs or Division Chiefs for candidates that are conditionally approved or not recommended for approval.

Assistant Director of Clinical Operations 3/2011 - 12/2013
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

- Worked closely with the Director of Clinical Operations to strategize long-term vision and processes for the Department's clinical activities. Interviewed all candidates for faculty positions and fellowships. Responsible for the yearly performance evaluations for 5 faculty members.

- Instrumental in the initiation of the Departmental Peer Review Process, a nationally recognized model of peer review and process improvement.

Emergency Medicine Residency Curriculum Committee 2011 - current
University of Massachusetts Medical School
Worcester, MA

- Responsible for overhaul of entire 18-month emergency medicine residency curriculum.

Peer Review Committee 2011 - current
Department of Emergency Medicine
University of Massachusetts Medical School

- A nationally recognized peer review process whose monthly meeting of approximately 12 individuals confidentially and anonymously reviews concerns of care. Feedback delivered to individual practitioners and findings presented at weekly departmental Morbidity and Mortality conference.

Medical Staff Executive Committee 2010 – 11/2024
UMass Memorial Medical Center
Worcester, MA

- Executive committee of the medical staff. Reviews and approves all hospital policies. Responsible for approval of medical staff privileges and recommending/monitoring physicians' compliance with Physician Health Services as needed.

Research Committee 2003 - current
Department of Emergency Medicine
University of Massachusetts Medical School
Worcester, MA

- Committee charged with providing guidance and vision for Departmental research; reviewing internal and extramural proposals; and awarding internal funding.

Emergency Medicine Residency Selection Committee 2002 - 2023
University of Massachusetts Medical School
Worcester, MA

- 21 years of service on committee that reviews, interviews, and ranks medical students applying to UMass for emergency medicine through the NRMP Match. Chair of this committee from 2011-2019.

Chair of Physician Incentive Compensation Committee 2006 - 2011
Department of Emergency Medicine
UMassMemorial Health
Worcester, MA

- Responsible for the development and growth of the emergency medicine physician incentive compensation plan. Grew this plan from a total of $70,000 per year in 2005 to over $1.1 million in 2011 (and now up to nearly $2 million). Responsible for determination of incentive plan metrics, monitoring performance of those metrics across 70+ faculty, and yearly reporting of the metrics.

Procedural Sedation Committee 2004 - 2010
UMassMemorial Health
Worcester, MA

- Committee responsible for writing institutional policies regarding procedural sedation. Also responsible for reviewing quality data and any adverse events related to procedural sedation for the hospital and clinics.

National

Board of Directors – Immediate-Past President 5/2019 – 5/2020
Society for Academic Emergency Medicine

- Immediate-Past President of the 6700-member Society for Academic Emergency Medicine. Responsible for guiding the 9-member Board of Directors on overall strategic plan for the organization, as well as guiding a $4.5 million budget.

Board of Directors – President 5/2018 - 5/2019
Society for Academic Emergency Medicine

- President of the 6700-member Society for Academic Emergency Medicine. Responsible for guiding the 9-member Board of Directors on overall strategic plan for the organization, as well as guiding a $4.5 million budget.

Board of Directors – President-Elect 5/2017 - 5/2018
Society for Academic Emergency Medicine

- Elected to the President-Elect role of SAEM in March 2017. Will assume role of President in May 2018.

AAMC Standardized Video Interview Workgroup 1/2017 - 8/2019

- Member of workgroup convened by the AAMC to define rubric for scoring of the Standardized Video Interview (SVI) project. Furthermore, we analyzed interim data from a trial of the SVI and have

informed the AAMC on methods to improve the SVI, as well as creating a research agenda around the SVI.

National Academy of Medicine (NAM) 1/2017 – 8/2024
Clinician Well-Being Action Collaborative

- I represent the field of emergency medicine on this national collaborative involving the entire house of medicine. The mission of the NAM Clinician Well-Being Action Collaborative (chaired by Drs. Victor Zhou, Thomas Nasca, and Darrel Kirch) is to create a body of knowledge, research agenda, and implementation science to mitigate burnout amongst physicians, promote wellness, and return joy to the practice of medicine. I am one of just 3 emergency physicians involved in this national effort.

Board of Directors – Secretary-Treasurer 5/2016 – 5/2017
Society for Academic Emergency Medicine

- Member of the Board of Directors. Responsible for financial oversight of the largest academic emergency medicine society in the U.S., with annual budget of over $4 million. Participate in the strategic direction of the Society.

Board of Directors 2011 - 2013 & 2016 - 2019
Emergency Medicine Foundation

- Member of the Board of Directors of the EMF, a 501c3 research funding organization affiliated with the American College of Emergency Physicians. Responsible for directing areas of research focus as well as fund raising and approving grant funding of approximately $1 million per year.

Board of Directors 5/2014 – 5/2020
Society for Academic Emergency Medicine Foundation

- Member of the Board of Directors of the SAEM Foundation, a 501c3 research funding organization with a corpus of over $11 million. Responsible for directing areas of research focus as well as fund raising.

Board of Directors (member-at-large) 5/2014 - 5/2016
Society for Academic Emergency Medicine

- Member of the Board of Directors. Responsible for oversight and providing strategic direction for the largest academic emergency medicine society in the U.S.

Search Committee 10/2014 - 5/2015
CEO of the Society for Academic Emergency Medicine

- Member of 10-person search committee for new CEO of the Society for Academic Emergency Medicine. Resulted in the hiring of CEO Megan Schagrin.

Search Committee 9/2014 - 7/2015
Academic Emergency Medicine Editor-in-Chief

- Member of 6-person search committee for new Editor-in-Chief of Academic Emergency Medicine.

NIH Special Emphasis Panel Review Member 2012 - 2016

- Serves as review for NIH panel ZRG1 MDCN-B

Finance Committee 2011 - 2013

American College of Emergency Physicians

- Committee responsible for generating and approving ACEP's yearly budget of roughly $22 million. Interacted directly with ACEP's Executive Director, CFO, and Board of Directors.

Annual Meeting Program Committee 2008 - 2014
Society for Academic Emergency Medicine

- Co-chair of scientific subcommittee. Responsible for coordinating reviewers and reviewing more than 1,200 abstracts to the SAEM annual meeting. Responsible for organization of the entire scientific aspects of the meeting (determining oral presentations, poster presentations, assigning moderators, meeting room assignments at host hotels, etc.

Grants Committee 2004 - 2014
Society for Academic Emergency Medicine

- Responsible for reviewing grant applications to SAEM. Served as chair of the Institutional Research Training Grant category in 2010, the Education Research Grant in 2011, and the Spadafora Medical Toxicology Grant in 2012. Made recommendations for funding to the SAEM Board of Directors for grants totaling approximately $400,000/year.

Scientific Review Committee 2003 - 2011
American College of Emergency Physicians

- Responsible for reviewing grant applications to Emergency Medicine Foundation. Made recommendations for funding to the EMF Board of Directors for grants totaling more than $1,000,000/year.

Research Committee 2003 - 2004
Society for Academic Emergency Medicine

International

Southeast Asia Toxicology Research Consortium 2004 – 2019

Scholarly

Editorial Board 2019 - current
The Journal of Wellness

Editorial Board 2009 - current
Academic Emergency Medicine

Editorial Board 2009 - 2013
The Open Toxinology Journal

Editorial Board – founding member 2005 - 2011
Journal of Medical Toxicology

Manuscript reviewer for *JAMA; Academic Emergency Medicine; Annals of Emergency Medicine; Pediatrics; Journal of Emergency Medicine; Journal of Medical Toxicology; Clinical Toxicology; The Open Toxinology Journal; PLoS One*

Invited Attendance

Extracorporeal Removal of Toxins in Poisoning (ExTRIP) working group
Montreal, Canada, October 2019

American College of Medical Toxicology Chemical Agents of Opportunity symposium
Nashville, TN, May 2019

12th International Symposium on Protection Against Chemical Warfare Agents
Munich, Germany, April 2019

Western Regional SAEM Conference, Napa, CA, March 2019

NINDS CounterACT meeting, Boston, MA, June 2017

10th International Symposium on Protection Against Chemical Warfare Agents
Munich, Germany, April 2017

NINDS CounterACT meeting, Davis, CA, June 2016

NINDS CounterACT meeting, New York, NY, June 2015

NINDS CounterACT meeting, Denver, CO, June 2014

13th Congress of APAMT, Shenyang, China, September 2014

NIH Workshop on Neurologic Effects of Nerve Agents, Bethesda, MD, February 2014

NY Chapter of the American College of Emergency Physicians, Lake George, NY, July 2013

NINDS CounterACT meeting, Bethesda, MD June 2013

NINDS CounterACT meeting, San Francisco, CA June 2012

11th National Congress of the Iranian Society of Toxicology, Mashad, Iran, August 2011

5th Congress of APAMT, Colombo, Sri Lanka, August 2006

8th International Symposium on Protection Against Chemical Warfare Agents
Munich, Germany, May 2004

SIGNIFICANT MENTORING

Sneha Shah, MD	AMA Women's Section Award	2014
John Haran, MD	SAEM Research Training Grant	2014-2015
Chad Darling, MD	K23 from NHLBI	2010-2015

Romolo Gaspari, MD K08 from NINDS 2007-2012

COMMUNITY ACTIVITIES

St. John's High School Gala – Planning committee 2018 - 2020

- Assisted in securing sponsorships and auction items, selling tables, and planning the annual St. John's High School Galal. This event raised more than $250,000.

Yale Alumni Schools Committee – Central Mass 2009-2012

- Responsible for coordinating, assigning, and reviewing approximately 40 Yale alumni interviews of applicants to Yale University.

Spring Street School Chess Club 2009-2014

- Organized, coached, and facilitated the chess club for Spring Street School in Shrewsbury, Massachusetts, for grades 1-4. Increased participation in this chess club to nearly 40% of students in the school, creating the largest elementary chess club in New England.

Central Mass Heart Ball – Planning committee 2010 & 2011

- Responsible for securing sponsorships and auction items, selling tables, and planning the annual American Heart Association Ball. This event raises more than $300,000 annually.

TEACHING RESPONSIBILITIES

Grand Rounds/Invited Lectures
University of Vermont Grand Rounds. "Chest Pain Testing in the ED" December 11, 2017, Burlington, VT.

University of West Virginia Grand Rounds. "Rationale Testing in the ED" August 24, 2017, Morgantown, WV.

Society for Academic Emergency Medicine Annual Meeting, "Before Taking Care of Others You Must Take Care of Yourself" May 2017, Orlando, FL

Society for Academic Emergency Medicine Annual Meeting, "Accepting Risk and the Myth of Zero" May 2017, Orlando, FL

Falmouth Hospital Emergency Care Conference, "Emerging Drugs of Abuse and Testing Conundrums" March 2017, Falmouth, MA

University of Vermont Larner School of Medicine, Emergency Medicine Update, "Visual Toxicology". February 2017, Stowe, VT

University of Vermont Larner School of Medicine, Emergency Medicine Update, "Pattern Recognition in Toxicology". February 2017, Stowe, VT

North American Congress of Clinical Toxicology, "Neurotoxicology of Organophosphorus Pesticides". October 2016, Boston, MA

Controversies and Consensus in Emergency Medicine conference, "Safely Decreasing Stress Testing from the Emergency Department". September 2016, Northampton, MA

Society for Academic Emergency Medicine Annual Meeting, “Accepting Risk and the Myth of Zero” May 2016, New Orleans, LA

Society for Academic Emergency Medicine Annual Meeting, “Metacognition: How Physicians Think” May 2016, New Orleans, LA

Boston Medical Center faculty retreat, “Wellness, Resiliency, and Empathy”, April 2016, Newport, RI

American College of Emergency Physicians Annual Meeting, “Beyond the Bends” October 2015, Boston, MA

American College of Emergency Physicians Annual Meeting, “Dangerous Drug Interactions” October 2015, Boston, MA

American College of Emergency Physicians Annual Meeting, “Nature’s Deadliest Creatures” October 2015, Boston, MA

ACEP Toxicology Interest Group, “From Benchtop to Sri Lanka: One Toxicologists Journey” October 2015, Boston MA

Society for Academic Emergency Medicine Annual Meeting, “Do Your Patients Know You Care? Methods to Convey Empathy” May 2015, San Diego, CA

American College of Emergency Physicians Annual Meeting, “Dangerous Drug Interactions” October 2014, Chicago, IL

American College of Emergency Physicians Annual Meeting, “Environmental Emergencies” October 2014, Chicago, IL

Rhode Island Hospital/Brown University. “How Physicians Think” September 2014, Providence, RI.

Asia Pacific Association of Medical Toxicology, “Translational Therapies for Acute Organophosphorus Inhibitor Poisoning” September 2014, Shenyang, China.

Sapporo Medical University, “Novel Therapies for Acetylcholinesterase Inhibitor Poisoning” September 2014, Sapporo, Japan.

Society for Academic Emergency Medicine Annual Meeting, “Metacognition: Thinking About How You Think” May 2014, Dallas, TX

American College of Emergency Physicians Annual Meeting, “Dangerous Drug Interactions That Can Kill Your Patients” October 2013, Seattle, WA

American College of Emergency Physicians Annual Meeting, “Cutting-Edge Ideas in Toxicology” October 2013, Seattle, WA

Albany Medical College Department of Emergency Medicine, “How to Give a Presentation” August 2013, Albany, NY

Boston Medical Center Department of Emergency Medicine. “Metacognition” August 2013, Boston, MA

New York chapter of the American College of Emergency Physicians: “New and Emerging Drugs of Abuse” July 2013, Lake George, NY

New York chapter of the American College of Emergency Physicians: “Drug-Drug Interactions in the Emergency Department” July 2013, Lake George, NY

American College of Emergency Physicians Annual Meeting: “What Goes Down, Must Come Up: Diving Medical Emergencies” October 2011, San Francisco, CA

American College of Emergency Physicians Annual Meeting: “Marine Envenomations” October 2011, San Francisco, CA

North Country Hospital: “Pattern Recognition in Adverse Drug Events” February 2011, Newport, Vermont

Washington University School of Medicine: ““Translational Research in Emergency” September 2010, St. Louis, MO

University of Massachusetts Medical School: “Translational Research in Emergency Medicine and Building an Academic Career” July 2009 Worcester, MA

Children’s Hospital Boston - Pediatric Emergency Medicine and Massachusetts Poison Control Center; “Acetylcholinesterase Inhibitors” May 2008, Boston, MA

University of Iowa, Department of Emergency Medicine. “Organophosphates and Chemical Nerve Agents.” November 2005, Iowa City, IA

University of Iowa, Department of Emergency Medicine. “Antidepressant Poisoning.” April 2006, Iowa City, IA

University of Iowa, Department of Emergency Medicine. “Pattern Recognition in Toxicology.” April 2006, Iowa City, IA

University of Massachusetts Medical School: “Translational Research in Emergency Medicine: from Benchtop to Sri Lanka” June 2007 Worcester, MA

Brigham and Women’s Hospital, Division of Emergency Medicine: “Cardiovascular Poisonings” May 2006, Boston, MA

Center for Disease Control and Prevention. Agency for Toxic Substances and Disease Registry. “Agents of Opportunity: Toxic Gases” March 2005, Hartford, CT

Brigham and Women’s Hospital, Division of Emergency Medicine: “Procedures in Toxicology” February 2005, Boston, MA

Baystate Medicine Center, Department of Emergency Medicine “Poison Control Center Functions” March 2004, Springfield, MA

Portsmouth Naval Medical Center: “Pattern Recognition in Toxicology” March 2003, Portsmouth, VA

Harvard School of Public Health: “Neurotoxicology” October 2003, Boston, MA

Classroom Lectures (selected)
University of Massachusetts Emergency Medicine Residency: “Toxicology In-Service Review” February 2016, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “How to Give a Presentation”

August 2015, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Toxicology In-Service Review” February 2015, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Metacognition”
June 2013, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Toxicology In-Service Review” February 2013, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Dysbarism”
Sept 2012, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Impact Factor and Bibliometric Indices”
July 2012, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “How to Give a Presentation”
Sept 2011, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Pattern Recognition in Toxicology”
July 2011, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Ethanol Forensics”
Apr 2011, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Acetaminophen Toxicity”
Aug 2007, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Endocrine Emergencies”
Feb 2007, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Pattern Recognition in Toxicology”
July 2006, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Toxic Alcohols”
April 2004, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Central Venous Access”
August 2003, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Introduction to the Poisoned Patient”
July 2003, Worcester, MA

Massachusetts College of Pharmacy: “Summertime Poisonings”
July 2003, Worcester, MA

Massachusetts College of Pharmacy: “Introduction to the Poisoned Patient”
May 2003, Worcester, MA

Emergency Medical Services: “A Trip Through the Medicine Cabinet”
December 2002, Williamstown, MA

University of Massachusetts Emergency Medicine Residency: “Acetaminophen”
August 2002, Worcester, MA

University of Massachusetts Emergency Medicine Residency: “Anti-hypertensive Poisonings”
January 2002, Worcester, MA

Clinical Teaching and Supervision
Responsible for all aspects of training for 36 emergency medicine residents

Oversees residents and medical students approximately 50 hours/month in the emergency department

Oversees 3 medical toxicology fellows and one emergency medicine resident per month on the toxicology consultation service

Participates in weekly toxicology conference for residents, fellows, and pharmacists

PAPERS IN PEER-REVIEWED JOURNALS

1. S Howard-Wilson, J Ching, S Gentile, M Ho . . . **Bird SB** et al. Efficacy of a Multimodal Digital Behavior Change Intervention on Lifestyle Behavior, Cardiometabolic Biomarkers, and Medical Expenditure: Protocol for a Randomized Controlled Trial. JMIR Research Protocols 13 (1), e50378

2. Ligibel JA, Goularte N, Berliner JI, **Bird SB**, Brazeau CMLR, Rowe SG, Stewart MT, Trockel MT. Well-being parameters and intention to leave current institution among academic physicians. *JAMA Open Network* 2023; 6: e2347894-e2347894

3. Ghannoum G, Gosselin S, Hoffman RS et al. Extracorporeal treatment for ethylene glycol poisoning: systematic review and recommendations from the EXTRIP workgroup. *Critical Care* 2023;27:56.

4. Lu D, Lee J, Alvarez A, Sakamoto J, **Bird SB**, Vandana S, Laa M, Nordenholz M, Manfredi R, Blomkalns Factors Driving Burnout and Professional Fulfillment Among Emergency Medicine Residents: A National Wellness Survey. *Acad Emerg Med Ed Training* 2022; 6:S5-S12.

5. Bouchard J, Yates C, Calello DP et al. Extracorporeal Treatment for Gabapentin and Pregabalin Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup. *Am J Kid Dis*. 2022;79: 88-104.

6. Lu D, Lee J, Alvarez A, Sakamoto J, **Bird SB**, Vandana S, Laa M, Nordenholz M, Manfredi R, Blomkalns A. Drivers of Professional Fulfillment and Burnout Among Emergency Medicine Faculty: A National Wellness Survey by the Society for Academic Emergency Medicine. *Acad Emerg Med* 2022; published online March 19, 2022. ttps://doi.org/10.1111/acem.14487

7. Ghannoum G, Berling I, Lavergne V et al. Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning. *Kid Interl* 2021;100:720-36.

8. Brower KJ, Brazeau CMLR, Kiely SC, et al. The Evolving Role of the Chief Wellness Officer in the Management of Crises by Health Care Systems: Lessons from the Covid-19 Pandemic. *NEJM Catalyst*. 2021; 5. DOI:https://doi.org/10.1056/CAT.20.0612.

9. Bouchard J, Shepherd G, Hoffman RS, et al. Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup. *Crit Care* 2021;25**:** 201-. https://doi.org/10.1186/s13054-021-03585-7.

10. Wong A. Hoffman RS, Walsh SJ, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol* 2021;59: 361-375.

11. Mowry JB, Shepherd G, Hoffman RS, et al. Extracorporeal Treatments for Isoniazid Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. *Pharmacotherapy* 2021; 00:1-16.

12. Berling I, King JD, Shepherd G, et al. Extracorporeal Treatment for Chloroquine, Hydroxychloroquine, and Quinine Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. *J Am Soc Nephrol* 2020 Oct;31(10):2475-2489. doi: 10.1681/ASN.2020050564

13. Nordenholz KE, Alvarez A, Lall MD, **Bird S**, Blomkalns AL. Optimizing Wellness in Academic Emergency Medicine. *J Wellness* 2020. DOI: 10.18297/jwellness/vol2/iss2/8

14. Gallahue FE, Deiorio NM, Blomkalns A, **Bird SB**, et al. The AAMC Standardized Video Interview – Lessons Learned from the Residency Selection Process. *Acad Med* 2020. doi: 10.1097/ACM.000000000000357

15. Melnyk BM, Kelly SA, Stephens J . . . **Bird SB**. Interventions to Improve Mental Health, Well-Being, Physical Health, and Lifestyle Behaviors in Physicians and Nurses: A Systematic Review. *Am J Health Prom*, 2020 Nov;34(8):929-941.

16. Greenberger SM, Finnell JT, Chang BP, Garg N, Quinn SM, **Bird SB,** et al. Changes to the ACGME Common Program Requirements and Their Potential Impact on Emergency Medicine Core Faculty Protected Time. *Acad Emerg Med Ed & Training*. Nov 23, 2019. ttps://doi.org/10.1002/aet2.10421

17. **Bird SB**, Hern HG, Blomkalns A et al. Innovation in Residency Selection: The AAMC Standardized Video Interview. *Acad Med*. 2019;94:1489-97. doi:10.1097/ACM.0000000000002705

18. Gallahue FE, Hiller KM, **Bird SB** et al. The AAMC Standardized Video Interview: Reactions and Use by Residency Programs During the 2018 Application Cycle. *Acad Med* 2019;94:1506-12. doi: 10.1097/ACM.0000000000002714

19. Dyrbye LN, Meyers D, Ripp J, Dalal N, **Bird SB**, Sen S. A pragmatic approach for organizations to measure health care professional well-being. *National Acad Medicine*, Oct 2018, pp 1-11.Doi.org/10.31478/201809g

20. Deiorio NM, Jarou ZJ, Alker A, **Bird SB**, et al. Applicant Reactions to the AAMC Standardized Video Interview During the 2018 Application Cycle. *Acad Med* 2019 Oct;94(10):1498-1505. doi: 10.1097/ACM.0000000000002842.

21. Jarou Z, Karl E, Alker A, **Bird SB**, et al. Factors Affecting Standardized Video Interview Performance: Preparation Elements and the Testing Environment. *EM Resident*, April 17, 2018.

22. **Bird SB**, Blaomkalns A, Deiorio NM, Gallague FE. Beyond test scores and medical knowledge: the standardized video interview, an innovative and ethical approach for holistic assessment of applicants. *Acad Med* 2018;93:151.

23. **Bird S**, Blomkalns A, Deiorio NM, Gallague FE et al. Stepping up to the plate: emergency medicine takes a swing at enhancing the residency selection process. *AEM Ed & Training* 2017;2: 61-5. Doi: 10.1002/aet2.10068.

24. Shah S, Church R, Butler M, **Bird SB**. Assessment of emergency medicine faculty milestone competencies. *Intl J Ed Res Tech* 2017; 8 (2): 1-7.

25. **Bird SB**. Neurologic and pregnancy effects of carbon monoxide exposure. *Toxicol Open Access*. 2017, 3:4. Doi: 10.4172/2476-2067.

26. Bunya N, Sawamoto K, Benoit H, **Bird SB**. The Effect of Parathion on Red Blood Cell Acetylcholinesterase in the Wistar Rat. *J Toxicol* 2016. doi.org/10.1155/2016/4576952

27. **Bird SB**, Krajacic P, Sawamoto K, Bunya N, Loro E, Khurana TS. Pharmacotherapy to protect the neuromuscular junction after acute organophosphate poisoning. *Proc Ann NY Acad Sci* 2016; 1674:86-93.

28. Marin JR, Lewiss RE, Shook JE, et al. Point-of-care ultrasonography by Pediatric Emergency medicine physicians. *Pediatrics* 2015;135:e1113-22.

29. Temple C, Gaspari R, **Bird S**. Caffeine reduces organophosphate induced respiratory failure; effect of caffeine on dichlorvos induced central respiratory failure in a rat model *Curr Topic Toxicol* 2015; 11, 15 – 21.

30. Reznek MA, Kotkowski KA, Arce MW, Jepson ZK, **Bird SB**, Darling CE. Patient safety incident capture resulting from incident reports: a comparative observational analysis. *BMC Emergency Medicine* 2015, **15**:6 doi:10.1186/s12873-015-0032-7.

31. Broach J, Krupa R, **Bird SB**, Manuell M. Regional preparedness for mass acetylcholinesterase inhibitor poisoning through plans for stockpiling and interhospital sharing of pralidoxime. *Am J Disaster Med*. 2014:9;4, 1-9. Doi:10.5055/ajdm.2014.0000

32. Jepson ZK,Darling CE, Kotkowski KA, **Bird SB**, Arce MA, Volturo GA, Reznek MA. Emergency department patient safety incident characterization: an observational analysis of the findings of a standardized peer review process. *BMC Emergency Medicine* 2014,14:20-27.DOI:101186/1471-227X-14-20

33. Neavyn MJ, Blohm E, Babu KM, **Bird SB**. Medical marijuana and driving. *J Med Toxicol*. 2014; available online March 2014. DOI 10.1007/s13181-014-0393-4.

34. Jackson CJ, Carville A, Ward J, Mansfield K, Ollis DL, Khurana T, **Bird SB**. Use of OpdA, an Organophosphorus (OP) hydrolase, prevents lethalilty in an african green monkey model of acute OP poisoning. *Toxicol* 2014;317:1-5. doi: 10.1016/j.tox.2014.01.003

35. Sawamoto K, **Bird SB**, Katayama Y, Uemura S, Tanno K, Narimatsu E. Outcome from severe accidental hypothermia with cardiac arrest resuscitated with extracorporeal cardiopulmonary resuscitation. *Am J Emerg Med* 2014; 32(4):320-4. doi: 10.1016/j.ajem.2013.12.023.

36. Neavyn MJ, Boyer EW, **Bird SB**, Babu KM. Sodium acetate as a replacement for sodium bicarbonate in medical toxicology. *J Med Toxicol*. 2013 Sep; 9(3):250-4 doi: 10.1007/s13181-013-0304-0.

37. Darling CE, Smith CS, Sun JE, Klauke CG, Lerner J, Cyr J, Paige P, Paige PG, **Bird SB**. Cost reductions associated with a quality improvement initiative for patients with ST-elevation myocardial infarction. *Jt Comm J Qual Patient Saf*. 2013;39:16-21. PMID 23367648

38. Dunn C, **Bird S**, Gaspari R. Intralipid Fat emulsion decreases respiratory failure in a rat model of parathion poisoning. *Acad Emerg Med*. 2012;19:504-509.

39. Rosenbaum C, **Bird SB**. Non-muscarinic targets of organophosphorus pesticides. *J Med Toxicol* 2010 Dec;6(4):408-12.

40. Jackson CJ, Scott C, Carville A, Mansfield K, Ollis DL, **Bird SB**. Pharmacokinetics of OpdA, an organophosphorus hydrolase, in the African green monkey. *Biochem Pharmacol* 2010;80:1075-9.

41. Gresham C, Rosenbaum C, Gaspari R, Jackson CJ, **Bird SB**. "Kinetics and efficacy of an organophosphorus hydrolase in a rodent model of methyl-parathion poisoning. *Acad Emerg Med* 2010; 17:736-740.

42. **Bird SB**, Dawson A, Ollis D. "Enzymes and bioscavengers for prophylaxis and treatment of organophosphate poisoning" *Front Biosci* 2010; S2:209-220.

43. Rosenbaum CR, Church R, **Bird SB**. "Timing and frequency of physostigmine redosing for antimuscarinic toxicity" *J Med Toxicol* Published online April 20, 2010. DOI 10.1007/s13181-010-0077-7

44. Weibrecht K, Dayno M, Darling C, **Bird SB**. ""Liver aminotransferases are elevated with rhabdomyolysis in the absence of liver injury" *J Med Toxicol.* Published online April 21, 2010. DOI 10.s131181-010-0075-9

45. **Bird S,** Sutherland T, Gresham C, Oakeshott J, Eddleston M. "OpdA, a recombinant bacterial organophosphorus hydrolase, prevents lethality in rats after poisoning with highly toxic organophosphours pesticides" *Toxicol* 2008;247: 88-92.

46. **Bird SB**. "Impact factors, H indices, and citation analyses in toxicology Journals" *J Med Toxicol* 2008;4: 261-274.

47. **Bird S,** Sivilotti M. "Self-plagiarism, textual reuse, and the intent to mislead." *J Med Toxicol* 2008;4: 69-70.

48. Young K, **Bird S**, et al. "Productivity and career paths of previous recipients of SAEM research grant awards" *Acad Emerg Med* 2008; 15: 560-566.

49. Ali F, Boyer E, **Bird S**. "Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics" *Alcohol* 2008;42: 213-218.

50. Kent K, Ganetsky M, Cohen J **Bird S**. "Non-fatal ventricular dysrhythmias associated with severe salicylate toxicity" *Clin Toxicol* 2008; 46: 297-299.

51. **Bird SB**, Rosenbaum CR. "Onset of symptoms after methadone overdose." Am J Emerg Med. 2008;26: 242.

52. Miller M, Navarro M, **Bird S**, Donovan J. "Antiemetic use in acetaminophen poisoning: how does the route of N-acetylcysteine administration affect utilization?" *J Med Toxicol* 2007; 3: 152-156.

53. Sivilotti MLA, **Bird SB**, Lo JCY, Dickson EW. "Multiple centrally-acting antidotes protect against severe organophosphate toxicity" *Acad Emerg Med* 2006; 13: 359-364.

54. **Bird SB**, Lane DR. "House officer procedure documentation using a personal digital assistant: a longitudinal study" *BMC Medical Informatics and Decision Making* 2006; 6.

55. Weizberg M. Su M. Mazzola JL. **Bird SB**. Brush DE. Boyer EW. "Altered mental status from olanzapine overdose treated with physostigmine" *Clin Toxicol.* 44(3):319-25, 2006.

56. Babu KM, McCormick M, **Bird S**. "Pediatric dietary supplement use – an update. *Clin Ped Emerg Med* 2005; 6: 85-92.

57. Mazzola JL, **Bird SB**, Brush DE, Aaron CK, Boyer EW. "Levofloxacin-related seizure activity in a patient with Alzheimer's disease: assessment of potential risk factors" *Clin Psychopharm* 2005;25:287-288.

58. Brush DE, **Bird SB**, Boyer EW. "γ-Hydroxybutyrate use in older adults." *Ann Intern Med* 2004; 140:W70-71.

59. DE Brush, **SB Bird**, EW Boyer. "Monoamine oxidase inhibitor poisoning resulting from internet misinformation on illicit substances." *J Tox Clin Tox* 2004;42:191.

60. **Bird SB,** Boyer EW. "The pharmacology and toxicology of ranolazine: a new metabolic modulator" *IJMT* 2003;6.

61. Dickson EW, **Bird SB**, Gaspari R., Boyer E, Ferris C. "Diazepam attenuates central respiratory depression due to organophosphate poisoning". *Acad Emerg Med* 2003;10:1303-1306.

62. **Bird SB**, Gaspari R, Dickson EW. "Early death due to acute, severe organophosphate poisoning is a centrally mediated process". *Acad Emerg Med* 2003;10:295-298.

63. **Bird SB**, Gaspari RJ, Lee WJ, Dickson EW. "Diphenhydramine as a protective agent in severe organophosphate poisoning" *Acad Emerg Med* 2002 9:1369-1372.

64. Bonkovsky H, Azar R, **Bird S**, Szabo G, Banner B "Severe cholestatic hepatitis caused by thiazolidinediones: risks associated with substituting rosiglitazone for troglitazone" *Digest Dis Sci* July 2002;44:1632-1637.

65. **Bird SB**, Dickson EW. "Clinically significant Changes in pain along the visual analog scale" *Ann Emerg Med.* 2001;38:639-643.

66. **Bird SB**, Zarum RS, Renzi FP. "Emergency medicine resident procedure documentation using a handheld computerized device" *Acad Emerg Med.* 2001;8:1200-1203

TEXTBOOK EDITOR

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Toxicology section editor. Lippincott. 9th Ed.

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Toxicology section editor. Lippincott. 8th Ed.

Emergency Medicine Research Handbook for Residents and Medical Students. Emergency Medicine Residents' Association. 1st Ed.

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Toxicology section editor. Lippincott. 7th Ed.

Aghababian's Emergency Medicine: The Core Curriculum. Section editor of 25 chapters. Jones and Bartlett, 2nd Ed.

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Toxicology section editor. Lippincott. 6th Ed.

Aghababian's Emergency Medicine: The Core Curriculum. Section editor of 25 chapters. Jones and Bartlett, 1st Ed.

TEXTBOOK CHAPTERS

Bird SB. "Acetaminophen Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 9th edition.

Bird SB. "Anticonvulsant Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 9th edition.

Bird SB. "Antipsychotic Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 9th edition.

Bird SB. "Antiarrhythmic Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 9th edition.

Bird SB. "Chromium" Goldfrank L. et al., editors. *Goldfrank's Toxicologic Emergencies,* McGraw Hill. 10th edition.

Bird SB. "Acetaminophen Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 8th edition.

Bird SB. "Anticonvulsant Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 8th edition.

Bird SB. "Antipsychotic Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 8th edition.

Bird SB. "Antiarrhythmic Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 8th edition.

Bird SB. "Chromium" Goldfrank L. et al., editors. *Goldfrank's Toxicologic Emergencies,* McGraw Hill. 9th edition.

Bird SB. "Organophosphates and Carbamates" Aghababian R. editor. *Emergency Medicine: The Core Curriculum.* Jones & Bartlett, 2nd edition.

Bird SB. "Acetaminophen Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 7th edition.

Bird SB. "Antipsychotic Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 7th edition.

Bird SB. "Anticonvulsant Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 7th edition.

Bird SB. "Beta Blockers" Shannon M. et al., editors. *Clinical Management of Poisoning and Drug Overdose*, WB Saunders. 4th Ed.

Bird SB. "Organophosphates and Carbamates" Aghababian R. editor. *Emergency Medicine: The Core Curriculum.* Jones & Bartlett, 1st edition.

Bird SB. "Chromium" Goldfrank L. et al., editors. *Goldfrank's Toxicologic Emergencies,* McGraw Hill. 8th edition.

Bird SB. *Organophosphates and Carbamates*. UpToDate, 2004-present.

Bird SB. *Manual of Overdoses and Poisonings*. Linden, Rippe, and Irwin, Eds. 1st edition. Lipipincott Williams & Wilkins, Philadelphia, 2005. **Author of 12 chapters.**

Bird SB. "Acetaminophen Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 6th edition.

Bird SB. "Anticonvulsant Poisoning" *Intensive Care Medicine*. Rippe, and Irwin, Eds. 6th edition.

ABSTRACTS (selected presentations at national or international meetings)

1. Bunya N, Benoit H, Krajacic P, Loro E, Gaspari R, Khurana T, **Bird SB**. Pancuronium Improves Survival in a Rat Model of Acute Parathion Poisoning. May 2016, SAEM Annual Meeting, New Orleans, LA

2. Shah SH, **Bird SB**. Do Your Patients Know You Care? SAEM Annual Meeting 2015, San Diego, CA.

3. Bunya N, Benoit H, Krajacic P, Loro E, Gaspari R, Khurana T, **Bird SB**. Development of a rodent model of the Intermediate Syndrome. June 2015, NY Academy of Sciences, NY.

4. Bunya N, Sawamoto K, Benoit H, Gaspari R, Khurana T, **Bird SB**. Novel Neuromuscular Protection to CounterACT Organophosphorus (OP) Poisoning. CounterACT meeting 2014, Denver, CO.

5. Shah SH, Heitmann D, Mangolds V, Zgurzynski P, **Bird SB**. Evaluating the Implementation of an Interprofessional Team STEPPS Curriculum for Medical Students Using High Fidelity Simulation. CORD Annual Meeting 2014, New Orleans, LA.

6. Shah SH, Church R, **Bird SB**. Evaluating Faculty Milestone Competencies. CORD Annual Meeting 2014, New Orleans, LA.

7. Sawamoto K, Krajacic P, McCall J, DeLa Puente R, Ford-Webb T, Gaspari R, Khurana T, **Bird SB**. Novel Neuromuscular Protection to CounterACT Organophosphorus (OP) Poisoning. CounterACT meeting 2012, San Francisco, CA

8. **Bird SB**, Carville A, Mansfield K, Ollis D. Use Of An Organophosphorus Hydrolase Prevents Lethality In An African Green Monkey Model Of Acute Organophosphorus Poisoning. SAEM 2011 Annual Meeting, Boston, MA

9. Sharma K, Nelson L, Kurt K, **Bird S**, Brent J, Wax P. The Practice of Medical Toxicology in the US. NACCT Annual Meeting 2010, Denver, CO.

10. Weibrecht K, Dayno M, Darling C, **Bird S**. Liver aminotransferases are elevated with rhabdomyolysis in the absence of liver injury. NACCT Annual Meeting 2009, San Antonio, TX.

11. Rosenbaum C, **Bird S**. Timing and Frequency of Physostigmine for Anticholinergic Toxicity. NACCT Annual Meeting 2008, Toronto, Canada.

12. Acute Hepatotoxicity Associated with Amiodarone Administration Courtney J, Ganetsky M, **Bird SB**, Boyer EW. Clin Toxicol 2006; 44.

13. Isoniazid-Induced Psychosis in an Adolescent Male Gresham HW, Babu KM, Ali F, **Bird SB**, Boyer EW. Clin Toxicol 2006; 44.

14. Non – Fatal Cardiac Dysrhythimias Associated with Severe Salicylate Toxicity Kent KJ, Cohen JE, Ganetsky M, **Bird SB.** Clin Toxicol 2006; 44.

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23. Lane DR, **Bird SB**, Zarum RS. Documentation of Emergency Medicine Resident Procedures Using a Personal Digital Assistant. Acad Emerg Med 2003;10:537-538.

24. **Bird SB**, Eddleston M, Sutherland TD, Ollis D. Pharmacokinetics of an Organophosphorus Hydrolase in the African Green Monkey. SAEM 2008 Annual Meeting, New Orleans, LA.

25. **Bird SB**, Gresham H, Sutherland T, Eddleston M. Use of a Recombinant Bacterial Hydrolase for Acute Dichlorovos Poisoning. NACCT 2006 Annual Meeting, San Francisco, CA

26. **Bird SB**, Gresham H, Sutherland T, Eddleston M, Eyer P. Use of a Recombinant Bacterial Hydrolase for Acute Parathion Poisoning. SAEM 2006 Annual Meeting, San Francisco, CA.

27. **Bird SB**, Gaspari RJ, Aaron CK, Boyer EW, Dickson EW. Synergistic Effects of Glycopyrrolate, Ipratropium, and Diazepam on Mortality in a Rat Model of Lethal Organophosphate Poisoning. European Association of Poison Control Centres and Toxicologists 2003 annual meeting, Rome, Italy.

28. **Bird SB**, Mazzola JL, Boyer EW, Brush DE, Aaron CK. A Prospective Evaluation Of Abbreviated Oral N-Acetylcysteine (NAC) Therapy For Acetaminophen (Paracetamol) Poisoning. European Association of Poison Control Centres and Toxicologists 2003 annual meeting, Rome, Italy.

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31. **Bird SB**. Critical Care Toxicology: Organophosphate Poisoning. 2002 North American Congress of Clinical Toxicology, Palm Springs, CA.

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33. **Bird SB**, Gaspari RJ, Lee WJ, Dickson EW. Diphenhydramine as a Protective Agent in Severe Organophosphate Poisoning. Acad Emerg Med 2002;9:357.

34. **Bird SB**. Case Presentation Competition, 2002 Society for Academic Emergency Medicine annual meeting, St. Louis, Missouri.

35. **Bird SB**, Zarum RS. Emergency Medicine Resident Procedure Documentation is Not Increased Using a Handheld Computerized Device. 2002 Society for Academic Emergency Medicine annual meeting, San Francisco, CA.

36. **Bird SB**, Ni Y. Comparison of a Numeric Rating Scale and the Visual Analog Scale in Extremity Pain. American College of Emergency Physicians 2001 Annual Meeting, Las Vegas, NV.

37. **Bird SB**, Sullivan J, Mangolds G, Schmidt E, Nichols C, Dickson EW. Clinically Significant Changes in Pain Along the Entire Visual Analog Scale. American College of Medical Toxicology 2001 annual meeting, San Francisco, CA.

FUNDING (completed)

"A Fitbit Digital Health Intervention in the UMass ACO" $ 100,000
Jan 2021-Dec 2021
Massachusetts Digital Health Right Care 4 You Grant Program

"RCT of Wellness Coaches to Decrease Burnout" $ 12,000
Jan 2020-Dec 2020
Carl Atkins Risk Management Grant
UMassMemorial Healthcare

"Development of a Peer Support Network" $ 10,000
June 2016-May 2017
Carl Atkins Risk Management Grant
UMassMemorial Healthcare

"Pharmacotherapy to counterACT parathion-induced NMJ dysfunction"
Principal Investigator: **Steven B. Bird, MD**
U01 NIH/NINDS $3,082,749
Sept 2013 – Aug 2016

"Novel Neuromuscular Protection to CounterACT Acute Organophosphate Poisoning"
Principal Investigator: **Steven B. Bird, MD**
R21 NIH/NINDS $ 823,588
Oct 2011 – Sept 2013

"Use of a bacterial OP hydrolase antidote for parathion poisoning"
Principal Investigator: **Steven B. Bird, MD**
R21 NIH/NIEHS $ 446,875
Aug 2007 – Aug 2009

"Functional MRI Assessment of Acute Organophosphate Poisoning"
Principal Investigator: **Steven B. Bird, MD**
K08 NIH/NIEHS
Dec 2004 - Dec 2008 $ 580,669

"Recombinant Organophosphate Hydrolase for Acute Parathion Poisoning"
Principal Investigator: **Steven B. Bird, MD**
American College of Medical Toxicology
July 2005 – June 2006 $ 7,500

"Recombinant Organophosphate Hydrolase for Acute Dichlorvos Poisoning"
Principal Investigator: **Steven B. Bird, MD**
Emergency Medicine Foundation
July 2005 – June 2006 $ 5,000

"Ipratropium bromide as a treatment of organophosphate toxicity"

Principal Investigator: **Steven B. Bird, MD**
Emergency Medicine Foundation Resident Research Grant Award
2001 – 2002 $ 5,000

Appendix B

Steven B. Bird, MD

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Shrewsbury, Massachusetts 01545

List of all cases in which, during the previous 4 years, I have testified as an expert at trial or by deposition.

Howe v. Tiffany Warren and Ascension Medical Group; Case No. 2022-CV-944
In the 18th Judicial District Court of Sedgwick Co, Kansas
Deposition: November 2024

Garcia v. Webb County; Case No. 5-23-CV-00137
In the Southern District of Texas
Deposition: November 2024

Hodys v. Barnes; Case No. PC2017-5776
In the Superior Court of Providence, Rhode Island
Deposition: October 2024

Kimbrow v. Walgreens; Case No. 2023-L-0005405
In the Circuit Court of Cook County, Illinois
Trial: September 2024

Gross v. Walgreens; Case No. 2023-L-000469
In the Circuit Court of Cook County, Illinois
Trial: July 2024

Joiner v. Walgreens; Case 2023-L-004568
In the Circuit Court of Cook County, Illinois
Trial: July 2024

Valadez v. GSK; Case No. 2023-L-000483
In the Circuit Court of Cook County, Illinois
Trial: May 2024

Patrick Feindt, Jr. v. United States of America; Case No. 1:22-cv-397-LEK-KJM
In the District Court of Hawaii
Trial: May 2024

Mejia v. Stanford Hospital; Case No. FST-CV20-6046034S
In the Superior Court for Judicial District of Stamford/Norwalk of Connecticut
Trial: March 2024.

Hankins v. Jenkins; Case No. 2:22-CV-01590.
In the United States District Court for the Northern District of Alabama

Trial: March 2024

Kimbrow v. Walgreens; Case No. 2023-L-0005405
In the Circuit Court of Cook County, Illinois
Deposition: March 2023

Valadez v. GSK; Case No. 2023-L-000483
In the Circuit Court of Cook County, Illinois
Deposition: January 2023

Kasza v. Walgreens et al; Case No. 2023-L-005404
In the Circuit Court of Cook County, Illinois
Deposition: December 2023

Valdes v. GSK; Case No. 2021-021945-CA-01
In the 11th Judicial Circuit for Miami-Dade County Florida
Deposition: December 2023

Williams v. Walgreens et al.; Case No. 2023-L-004599
In the Circuit Court of Cook County, Illinois
Deposition: December 2023

Feindt v. United States of America: Case No. 22-cv-297lLEK-KJM
In the United States District Court of Hawaii
Deposition: November 2023

Wilson v. GSK; Case No. 22-CA-000284
In the 13th Judicial Circuit for Hillsborough County Florida
Deposition: November 2023

Hall v. Baptist Easley; Case No. 2018-CP-23—01576
In the Circuit Court for Greenville County of South Carolina
Trial: October 2023

Reinhart v. Short Mountain Trucking; Case No. 3:21-CV-03122
In the United States District Court for the Central District of Illinois, Springfield Division
Deposition: August 2023

Pagan v. Saranita; Case No. 12-CA-424 2015CA00424
In the Fifth Judicial Circuit Court for Lake County of Florida
Trial: July 2023

Heinrich v. Serens; Case No. 2904978/2018
In the Supreme Court for Onondaga County of New York
Trial: July 2023

Hall v. Baptist Easley; Case No. 2018-CP-23—01576
In the Circuit Court for Greenville County of South Carolina
Deposition: July 2023

Cooper v. Advocate Christ; Case No. 2019L004866
In the Circuit Court for Cook County of Illinois
Deposition: May 2023

Richey v. CSX Transportation; Case No. 19-CI-007780
In the Jefferson Circuit Court of Kentucky, Division Five
Deposition: April 2023

Bowditch v. MedStar; Case No. 2021 CA 003778 M
In the Superior Court in Washington D.C.
Deposition: April 2023

Pimentel v. HUMC; Case No. BER-L-93-20.
In the Superior Court for Bergen County of New Jersey
Deposition: January 2023

Devani v. Honor Health; Case No. CV2021-050489
In the Superior Court for Maricopa County of Arizona
Deposition: November 2022

Ruepke v. BNSF Railroad; Case No. 2019-L-007730
In the Circuit Court for Cook County of Illinois
Deposition: August 2022

Hartman v. Illinois Central Railroad; Case No. 2:20-cv-1633
In the United States District Court for the Eastern District of Louisiana
Deposition: June 2022

Hankins v. Jenkins; Case No. 2:22-CV-01590.
In the United States District Court for the Northern District of Alabama
Deposition: June 2022

Fravel v. Herard; Case No. 2021 L 32
In the Circuit Court of the 21st Judicial Circuit for Kankakee County of Illinois
Deposition: June 2022

Lloyd v. Memorial Hospital; Case No. 16-2019-CA-000961
In the Fourth Judicial Circuit for Duval County of Florida.
Deposition: June 2022

Shephard v. Mease; Case No. 17004700CI
In the Sixth Judicial Circuit for Pinellas County of Florida

Deposition: April 2022

State of Florida v. Baldie;
In the Ninth Judicial Circuit for Orange County of Florida
Trial: April 2022

Mejia v. Stanford Hospital; Case No. FST-CV20-6046034S
In the Superior Court for Judicial District of Stamford/Norwalk of Connecticut
Deposition: December 2021.

Florida v. Baldie; Case No. 2020-CF-004830-AO
In the Ninth Judicial Circuit for Orange County of Florida
Deposition: November 2021.

U.S. v. Carvajal; Case No. 1:20-CR-10023-GAO-1
In the United States District Court of Massachusetts
Trial: November 2021

Bacon v. AnMed Health Cannon; Case No. 2019-CP-39-00937
In the Circuit Court for Pickens County of South Carolina
Deposition: June 2021

Gordanier v. Waldo; Case No. 19AE-CC00286
In the Sixth Judicial Circuit for Platte County of Missouri
Deposition: May 2021

Rybar v. DePuy; Case No. 4:16-cv-01579-CEJ
In the Circuit Court for the City of St. Louis of Missouri
Deposition: April 2021

Steven B. Bird, MD