Exhibit 92

General Causation Expert Report of Timothy M. Mallon, M.D., M.P.H., MS.

Prepared by:

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I. Expert Qualifications

I am a Medical Doctor, board-certified in Preventive Medicine (Occupational Medicine). I hold a Bachelor's Degree in Biology from Clarkson University. I earned a Master's Degree in Public Health from Johns Hopkins University School of Public Health in 1985; a Master's Degree in Environmental Health from CUNY Hunter College in 1986; and a Master of Science in Natural Resource Policy and Management from the University of Michigan, Graduate School of Natural Resources in 1987. I attended medical school at the Syracuse Upstate Health Science Center in Syracuse, New York in 1991.

Currently, I hold an adjunct Assistant Professor position in Preventive Medicine at Uniformed Services University in Bethesda, MD, and I consult for the Veteran's Evaluation Services and the Health and Human Services Federal Occupational Health Program. Prior to my retirement from military service in 2016, I was a full professor in Preventive Medicine at the Uniformed Services University from July 2004 to July 2016.

For over six years (January 2013 – August 2019), I led a team of investigators studying the association between certain diseases and exposures to burn pit smoke in Iraq and Afghanistan. This team included researchers from the University of Rochester, Clarkson University, Emory University, Uniformed Services University, and the Armed Forces Health Surveillance Agency. We completed a health assessment of 200 service members exposed to burn pit smoke in Iraq and Afghanistan which generated over 30 publications in the peer-reviewed literature and won several awards, including grants from NIEHS, and the Department of Defense's Defense Health Agency, and earned recognition by the American College of Occupational and Environmental Medicine.

I was awarded a Lifetime Achievement Award for Leadership in Academic Medicine and Research in 2019 and the Army Surgeon General's Academic Excellence Award "the A-Designator" as the Residency Director in Occupational Medicine at the Uniformed Services University.

I served as the specialty editor for The Textbook of Military Medicine in Occupational and Environmental Medicine, the specialty editor of three supplements to the Journal of Occupational and Environmental Medicine in Workers Compensation Programs, and editor of two supplements on Burn Pit Exposures in Iraq and Afghanistan in 2016 and 2019.

I have authored or co-authored over 46 journal articles and written 23 book Chapters for the Textbook of Military Medicine and the Clinics of North America. I also served on the American Board of Preventive Medicine and the Accreditation Council for Graduate Medical Education Residency Review Committee in Preventive Medicine.

My training, expertise, and service have included work specific to environmental exposures and associated cancers. I trained specifically in toxicology, environmental health, environmental epidemiology, and cancer epidemiology as part of my coursework at Johns Hopkins University and CUNY. This included collaboration on epidemiologic studies of Agent Orange exposure, Non-Hodgkin's Lymphoma, and soft tissue Sarcoma. I also served on the Advisory Board for

several Residencies in Aerospace and Occupational and Environmental Medicine for the Air Force at Brook Air Force Base, Johns Hopkins Occupational and Environmental Medicine Residency Program in Baltimore Maryland, and the Navy School of Aerospace Medicine and Occupational Medicine in Pensacola, Florida.

I have taught over 200 residents in Occupational and Environmental Medicine as the Occupational and Environmental Medicine Residency Program Director at the Uniformed Services University in Bethesda, MD from 2005 to 2016. A copy of my curriculum vitae is attached as Exhibit 1.

II. Summary of Opinions

This report summarizes my medical expert opinions on the causal relationship between exposure to the chemicals in the water at the Camp Lejeune military base, including trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, and vinyl chloride, and the development of kidney cancer. My opinions are based on my professional education, training and experience, knowledge of the pertinent scientific and medical literature reasonably relied upon by others in my profession and the documents cited in this report. I am qualified to evaluate the scientific literature and to render opinions about exposure to these substances causing kidney cancer. I hold all of my opinions in this report to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement my report should new information become available.

I conclude to a reasonable degree of medical and scientific certainty that there is:

1. More likely than not a causal relationship between the toxic water at Camp Lejeune and kidney cancer.

2. More likely than not a causal relationship between exposure to TCE and kidney cancer.

3. As likely as not a causal relationship between exposure to benzene and kidney cancer.

4. More likely than not a causal relationship between exposure to PCE and kidney cancer.

5. As least as likely as not a causal relationship exists between exposure to Vinyl Chloride and kidney cancer;

6. More likely than not the effects of exposure to a combination of TCE, PCE, Vinyl Chloride and benzene is at least additive.

III. Causation Standard

I have reviewed the Camp Lejeune Justice Act of 2022 (CLJA)[1], which I understand to be the governing statute for the causation standard in this case. The CLJA requires that marines or family members bringing claims under the Act "show one or more relationships between the water at Camp Lejeune and the harm," by "producing evidence showing that the relationship between exposure to the water at Camp Lejeune and the harm is – (A) sufficient to conclude that

a causal relationship exists; or (B) sufficient to conclude that a causal relationship is at least as likely as not."[1]

"As likely as not" is a standard that is less rigorous than a "more likely than not" standard. I am familiar with these terms and how the terms are applied in the sciences of environmental science, toxicology, epidemiology and other sciences dealing with these same issues.

I also reviewed the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" dated January 13, 2017.[2] The ATSDR Report used four categories to classify the strength of the evidence for a causal relationship between the chemicals in the water at Camp Lejeune and various harms. The "Sufficient" and "Equipoise and Above" categories of this classification scheme employ the same language as the Camp Lejeune Justice Act: 1. Sufficient: The evidence is sufficient to conclude that a causal relationship exists. 2. Equipoise and Above: The evidence is sufficient to conclude that a causal relationship is *at least as likely as not*, but not sufficient to conclude that a causal relationship exists." The authors of the ATSDR describe how, in their view, each of these categories can be met. For example, for "equipoise and above evidence for causation," ATSDR states:

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., ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

3. A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence. ATSDR (2017 pp. 6-7)[2].

It is my opinion that these classifications are consistent with the sciences for which they apply (i.e., they are consistent with how the sciences of epidemiology, toxicology, and other related sciences apply these standards).

Based on my years of medical and epidemiological training and expertise, I am familiar with the term "equipoise," and find ATSDR's definition of "equipoise and above" or "at least as likely as

not" to be appropriate in this case. The explanations by ATSDR for how each category of classification can be met are similarly appropriate for this case and based on sound scientific principles and methodology. Moreover, I have reached many of my opinions in this case to a reasonable degree of medical and scientific certainty under a "more likely than not standard," which surpasses the "at least as likely as not" standard. I make clear throughout where each of my opinions are expressed under the "more likely than not" or "at least as likely as not" standard.

IV. Methodology Employed

The methodology I used to form my opinions in this case aligns with the standard practices that I and other experts utilize when conducting similar analyses. Specifically, my approach included the following:

- Conducting PubMed searches of peer-reviewed scientific literature examining associations between TCE, PCE, benzene, and/or vinyl chloride and kidney cancer.
- Searching the Cochrane database for systematic reviews and meta-analyses.
- Reviewing and analyzing reports from national and international agencies, such as the International Agency for Research on Cancer (IARC), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Toxicology Program (NTP), and the United States Environmental Protection Agency (EPA). This included a thorough review and evaluation of the studies cited within these reports.

I applied a weight-of-the-evidence approach, assigning varying levels of importance to studies based on their designs, methodologies, and limitations.

To contextualize my findings, I evaluated studies and reports using the Bradford Hill viewpoints, including strength of association, consistency, specificity, temporality, dose-response, plausibility, coherence, experiment, and analogy. While not every Bradford Hill viewpoint needs to be satisfied to establish causality, they serve as a valuable framework for causation determinations. In this report, I assess both the presence and strength of each Bradford Hill viewpoint and compare their relative significance to formulate my causation opinions.

Numerous epidemiological studies relevant to the association between TCE, PCE, Vinyl Chloride, and Benzene and kidney cancer are available. This section identifies and examines meta-analyses, cohort studies, case-control studies, ecologic/water-contamination studies, reports from national and international agencies, and Camp Lejeune-specific studies related to contaminants and kidney cancer. It is standard practice among experts in my field to consider data from each of these categories when conducting a causality assessment.

I also assess any relevant toxicology and mechanistic data that provide additional relevant information to this causal analysis.

V. Discussion

A. Kidney Cancer Generally

The kidneys are located in the back of the abdomen, with one kidney on each side of the spine. The Mayo Clinic describes kidney cancer as a [uncontrollable] growth of cells that starts in the kidneys.[3] In adults, Renal Cell Carcinoma (RCC) is the most common type of kidney cancer. Other, less common types of kidney cancer include Urothelial Carcinoma of the upper urinary tract or renal pelvis.

Kidney cancer is a change in the DNA of a person's cells. In normal cells, DNA tells the cells to grow at a set rate and tells the cells to die at a set time. When cells become cancerous, the DNA changes tell the cells to reproduce too fast. Further, mutated DNA in cancer cells does not tell the cells when to die as they normally would due to a lack of communication. This causes them to keep living when healthy cells would die. This results in too many cells forming in one place and they form together into a mass called a tumor. The tumor kills healthy parts of your body. In time, cancer cells can metastasize.

Urothelial Carcinoma of the renal pelvis is a form of kidney cancer that is found in the center of the kidney. These renal pelvis cancers generally have more in common with cancers of the bladder because of their make-up. More often than not epidemiology studies include these cancers with kidney cancers. In analyzing these studies, the risk ratios for kidney cancer versus renal pelvis cancers are similar. Additionally, risk ratios for kidney cancer epidemiology studies that include renal pelvis urothelial carcinomas with kidney cancer versus epidemiology studies involving kidney cancer that do not include these cancers are similar.

Consequently, kidney cancer epidemiology will be used in any causation analysis involving urothelial carcinoma of the renal pelvis. Further, TCE, PCE, vinyl chloride, and benzene are all known to cause renal pelvis urothelial carcinoma.

B. Chemicals in the Water at Camp Lejeune

The Hadnot Point treatment plant supplied drinking water to the main portion of Camp Lejeune, including most of the barracks and workplaces. Key water samples from Hadnot Point were collected in May and July 1982, December 1984, and throughout 1985. In 1982, TCE levels were as high as 1,400 ppb, and PCE levels reached 100 ppb. Benzene was first detected in samples collected in December 1984.[4]

The Tarawa Terrace treatment plant provided drinking water to the housing area and key sampling was taken in May and July 1982 and again from February 1985 onward. PCE levels in July 1982 reached 104 ppb and peaked at 215 ppb in February 1985.

The current U.S. EPA maximum contaminant levels (MCLs)[4] for TCE, PCE, and benzene are 5 ppb, established in 1989 for TCE and benzene and in 1992 for PCE. The MCL for Vinyl Chloride is 2ppb.

There was water modeling done related to the water at Camp Lejeune which showed TCE and PCE levels exceeding these limits as early as the 1950s. The wells with chemicals and toxins in them at Hadnot Point were shut down by February 1985.

For the cohort study of Marines and Navy personnel undertaken by Bove et. al. (2014a),[5] the exposure period was 1975–January 1985. The authors stated that during this time, the average monthly concentrations in Hadnot Point's water were 366 ppb for TCE, 15 ppb for PCE, 22 ppb for Vinyl Chloride and 5 ppb for benzene. In the Tarawa Terrace system, the median monthly concentrations were 85 ppb for PCE, 6ppb of Vinyl Chloride and 4 ppb for TCE. The monthly average of the two sites for TCE was 185 ppb, the monthly average for PCE was 50 ppb, the monthly average for VC was 13 ppb and the monthly average for benzene was 4 ppb.

As part of my review of the materials at issue in this case, I have reviewed the ATSDR water modeling reports that are publicly available as well as the exhibits to Plaintiff's expert Morris Maslia's expert report in this matter, both of which show the same data. The levels of toxins present at Camp Lejeune, as detailed by these reports, were hazardous to humans and known to cause kidney cancer.

C. Camp Lejeune Contamination Studies and Reports

1. ATSDR and Bove

ATSDR performed several epidemiological studies to determine if Marines and civilians on base at Camp Lejeune were at increased risk for cancers, including kidney cancer, as a result of exposure to water contaminated with trichloroethylene (TCE), perchloroethylene (PCE), benzene, and vinyl chloride.

In addition to the above four chemicals, the Camp Lejeune studies also include a total volatile organic compound (TVOC) exposure category and assessed the risk of kidney cancer based on exposure to TVOCs. In the Camp Lejeune studies section of this report, TVOC exposure will be discussed as well as its connection to kidney cancer. The TVOC exposure risk for kidney cancer will be analyzed using the Bradford Hill viewpoints.

Bove et. al 2014a[5] and 2014b[6] were two retrospective cohort mortality studies of Marines/Navy personnel and of civilian workers. The results of the studies showed a causal association between the water at Camp Lejeune and kidney cancer. Subsequently, there were additional studies and assessments of the evidence performed by Dr. Bove and ATSDR. ATSDR 2017,[2] ATSDR 2018,[7] Bove 2024.[8,9] These studies also found increases in risk of kidney cancer for people exposed to the water at Camp Lejeune. These studies used water modeling performed by Maslia et al. (2007)[10], (2013)[11] to reconstruct median monthly levels of contaminants in the water. These cohort studies found causal associations between the water at Camp Lejeune and elevated risks of death from kidney cancers. The studies compared the people exposed at Camp Lejeune with a similar unexposed cohort from U.S. Marine Corps Base Camp Pendleton. These studies are of particular importance because they assess the health effects of the precise exposure at issue in this case.

2. Bove F. et. al. (2014a) and (2014b) Cancer Mortality Study

Bove et. al. 2014a was a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and stationed at either Camp Lejeune or Camp Pendleton. Cancer mortality was determined from 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. The studies used the average monthly toxin levels at residences. The Camp Lejeune cohort had increased mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20). Kidney cancer was specifically elevated with an SMR of 1.35 (95% CI: 0.84, 2.16). Monotonic exposure responses were found for marines for cumulative exposure to total volatile organic compounds (TVOCs) and kidney cancer with a risk ratio for high cumulative exposure of 1.54 (95% CI: 0.63, 3.75) $\log_{10}\beta$ =0.06, 95% CI:-0.05, 0.17). Civilian employees were even higher at 4.44 (95% CI: 0.52, 38.19).

3. ATSDR 2017 Assessment of the Evidence at Camp Lejeune

In 2017 ATSDR conducted a Public Health Assessment of the drinking water contamination at Camp Lejeune. Dr. Bove and the ATSDR team described their assessment of the water contamination problem. They described how they determined the extent of the drinking water contamination.

ATSDR also performed an assessment of the evidence in 2017. One of the purposes of the 2017 ATSDR Assessment of the Evidence was to determine if there was evidence supporting a causal relationship of kidney cancer due to exposure to the water toxins at Camp Lejeune. The ATSDR Assessment of the Evidence report represents ATSDR's assessment of the state of evidence in 2017. ATSDR did not conduct any new meta-analyses. ATSDR placed high importance on studies conducted by other governmental agencies i.e., the U.S. Environmental Protection Agency (EPA 2011, 2012),[12,13] the National Toxicology Program (NTP 2015)[14] and the International Agency for Research on Cancer (2012),[15] (2014).[16] Importance was also given to prior meta-analyses. ATSDR concluded that there is "sufficient evidence for causation" for TCE and kidney cancer based on robust meta-analyses, recent cohort studies, and mechanistic evidence. For PCE, the ATSDR indicated that there is "below equipoise" for causation.

4. ATSDR (2018)[7] Morbidity Study of Marines, Civilian Employees at Camp Lejeune

The ATSDR (2018)[7] conducted a morbidity study of Marines and Navy personnel stationed at Camp Lejeune, North Carolina. This cohort at Camp Lejeune was compared with Marines and Navy personnel stationed at Camp Pendleton, California between 1972-1985. The study also included civilian workers at both bases. The purpose of the study was to evaluate whether exposure to contaminated drinking water at Camp Lejeune was associated with cancers and other diseases, including kidney cancer.

For Marines the OR for kidney cancer was 1.31 (95% CI: 0.86, 1.99) compared to Pendleton. For high residential exposures (≥90th percentile) to TCE and PCE, ORs were 1.42 (95% CI: 0.78, 2.58) and 1.79 (95% CI: 1.02, 3.12). There was also an examination of increased exposure levels

at Camp Lejeune without a comparison to Pendleton. Odds Ratios for high TCE and PCE exposure were 1.55 (95% CI: 0.95, 2.54) and 2.01 (95% CI: 1.29, 3.13) and monotonic exposure-responses were observed. Again, water distribution models were used alongside data on residential locations and duration of time on base at Camp Lejeune to estimate cumulative and average exposure to each chemical.

The OR for Civilian employees at Camp Lejeune as compared with those at Camp Pendleton was 1.52 (95% CI: 0.69, 3.35) for kidney cancer. The OR for high workplace exposures (≥90th percentile) to TCE/PCE among civilian employees at Camp Lejeune compared with those at Camp Pendleton was 13.92 (95% CI: 5.09, 38.10). For the analysis internal to Camp Lejeune civilian employees, the OR for high TCE/PCE exposure was 41.5 (95% CI: 10.2, 169.23), and a monotonic exposure-response relationship was observed.

5. Bove F. et. al. (2024)[8] Cancer Mortality Study

The Bove (2024)[8] cancer mortality study explored cancer mortality by type, utilizing a longer follow-up period than earlier investigations. The study extended the Camp Lejeune Cohort's follow-up from 2008 to 2018, comparing the cancer risks among military and civilian personnel stationed at Camp Lejeune and Camp Pendleton between 1972 and 1985.

Compared to Camp Pendleton Marines/Navy personnel, Camp Lejeune Marine and Navy personnel had a significantly increased risk of death from kidney cancer with a SMR of 1.22 (95% CI: 1.03, 1.45) (Table S2). The civilian workers analysis using Poisson regression noted an elevated SMR for kidney cancer death of 1.49 (95% CI: 0.76, 2.92). These results reinforce the conclusion that chemical exposure levels at Camp Lejeune were linked to a higher risk of death due to kidney cancer.

The study also analyzed kidney cancer risk relative to exposure duration, measured by time spent on base. For personnel with short-term exposure (3–6 months or 1–2 quarters), the risk ratio was 1.33 (95% CI: 0.95-1.86 (Table S.6). For medium-term exposure (2–7 quarters), the risk ratio was 1.23 (95% CI: 0.88–1.72). (Table S.6). These findings suggest that even short durations on base during the 1972–1985 period were linked to a higher risk of death due to kidney cancer. Similarly, individuals who were on base at different intervals but received a cumulative exposure equivalent to 2–7 quarters during that period faced comparable risks.

The authors concluded that these findings are relevant to all individuals exposed to contaminated drinking water at Camp Lejeune. They emphasized the need for continued monitoring to evaluate the long-term health consequences of exposure to these chemicals since most of the Camp Lejeune service members were younger than 65 years old.

6. Bove et. al. (2024)[9] Cancer Incidence Study

The Bove et al. (2024)[9] Cancer Incidence Study on Camp Lejeune personnel indicates that compared with Camp Pendleton, Camp Lejeune Marines/Navy personnel had an adjusted elevated standardized incidence ratio (SIR) of 1.12 (95% CI: 0.65-2-13) (Bove 2024[9]) for renal cell carcinoma and renal pelvis cancer which had an adjusted elevated risk ratio of 1.12 (95%CI:

0.95-1-18)(Bove 2024[9]) for civilians. Civilians also had elevated RCC findings. These findings suggest that individuals exposed to contaminated water at Camp Lejeune during 1975–1985 were above equipoise elevated risk of developing kidney cancer. The evidence supports the causal association for kidney cancer following exposure to the drinking water at Camp Lejeune as likely as not.

The study also analyzed kidney cancer risk relative to exposure duration, measured by time spent on base. The category for low duration was 1-6 quarters. The medium duration of exposure was 7-10 quarters on base, and the high duration of exposure was over 10 quarters on base. For personnel with short-term exposure, the risk ratio for RCC was 1.12 (95% CI: 0.91-1.38 (Bove 2024[9] Table 5). For medium-term exposures, the risk ratio for RCC was 1.16 (95% CI: 0.86–1.55). These findings suggest that even short durations on base during the 1972–1985 period were linked to a higher risk of kidney cancer.

7. Rosenfeld et al. (2024)[17]

Rosenfeld et al. (2024)[17] used a risk assessment to determine if there were increased cancer risks for persons exposed to the drinking water at Camp Lejeune. The authors concluded that even just one month on base from 1980 to 1984 was causally related to an increased kidney cancer risk.

The study supports an association between the contamination levels in Camp Lejeune's water and hazard to humans, including kidney cancer.

8. Applying Bradford Hill Viewpoints for TVOC Exposures

a. Strength of Association

Bove et. al 2014a[5] and 2014b[6] support a causal association between TVOCs at Camp Lejeune and kidney cancer. There was a monotonic exposure trend for cumulative exposure to TVOCs for marines and kidney cancer with a risk ratio for high cumulative exposure of 1.54 (95% CI: 0.63, 3.75) $\log_{10} \beta$ =0.06, 95% CI:-0.05, 0.17). The risk for civilian employees was even higher at 4.44 (95% CI: 0.52, 38.19). The authors concluded that elevated hazard ratios existed for death from kidney cancer in the military and civilian cohorts.

b. Consistency

The consistency viewpoint is supported by findings across all studies involving Camp Lejeune by Bove and ATSDR, including both cohort studies in Marines and Navy personnel at Camp Lejeune and the Cohort Study of Civilian employees at Camp Lejeune. This consistency across these many studies supports the causal relationship between TVOCs and kidney cancer.

c. Specificity

The specificity viewpoint is hard to meet because exposures to the relevant chemicals can cause a variety of different medical conditions. However, epidemiological evidence demonstrates a clear and specific association between TVOC exposure and kidney cancer, distinguishing it from

other exposures and outcomes. Bradford Hill acknowledged that while specificity is not a strict requirement, a more specific association strengthens the probability of causation.

While TVOC exposure may also be associated with other diseases, the evidence presented here consistently shows that kidney cancer is more strongly linked to TVOC exposure compared to other outcomes. This viewpoint is limited because of the number of potential diseases that are known to be caused by these chemicals, but does provide some evidence of causation.

d. Temporality

The temporality viewpoint is unequivocally satisfied in this case, as all studies demonstrating an association between TVOC exposure and kidney cancer confirm that the exposure occurred prior to the onset of disease. This criterion is foundational to causal inference because, as Bradford Hill emphasized, the cause must precede the effect.

e. Exposure-Response

As noted in the Bove cohort study from 2014 listed above, cumulative TVOC exposure was noted to have a significant exposure response relationship with kidney cancer risk. There were other monotonic responses found in these studies as well. In my opinion, the evidence in support of this criterion is present, and strong.

f. Biological Plausibility

The biological plausibility of the chemicals in the water at Camp Lejeune causing kidney cancer are described in other areas of the report. However, to summarize, both TCE and PCE show consistent genotoxicity and their ability to induce epigenetic modifications strongly support biological plausibility. Similarly, TVOCs (a mixture of PCE and TCE along with other chemicals) in the drinking water at Camp Lejeune would also cause metabolism disruption, activation of pathway intermediates, and development of genetic damage that leads to kidney cancer development. There are also animal studies that support that the toxins in the Camp Lejeune water are causally related to kidney cancer. Again this is discussed in other parts of the report.

Thus, the noted mechanistic alterations strengthen the biological plausibility of TVOCs as a cause of kidney cancer, complementing the results from the epidemiological findings. Thus, it is my opinion the evidence for this criterion is strong.

g. Coherence

The coherence criterion evaluates whether epidemiological findings align with biological and toxicological knowledge. The Bove 2014a and Bove 2014b Camp Lejeune studies showed an association between TVOCs and kidney cancer. The other Camp Lejeune water studies also support this causation analysis. Mechanistic and animal studies confirm that TVOCs (containing TCE and PCE) demonstrate genotoxicity and genetic changes that aligns with these increased kidney cancer risks.

h. Experimental Evidence

While human experimental evidence is unethical to obtain, animal studies robustly demonstrate that TCE induces genotoxic effects. Further, the epidemiological studies cited above from Camp Lejeune support a causal relationship between TVOCs and kidney cancer. This supports the role of TVOCs in carcinogenesis.

i. Analogy

Metabolic pathways of TVOCs (including TCE and PCE) are similar. Major metabolites of TCE and PCE include the cytochrome P450-mediated oxidation and GSH conjugation. The metabolites include oxalate; trichloroacetyl chloride; and trichloroethanol O-glucuronide. Cichocki JA, et. al. (2016)[17a]. Pulmonary uptake of both chemicals is also rapid, with steady-state levels being attained within a few hours after the start of exposure (IARC, 2014). Both TCE and PCE break into lipid-containing tissue beds when absorbed into the body.

The TVOCs at issue have qualitatively similar metabolic schemes in rodents and humans (IARC, 2014). Metabolism of TCE and PCE can result in both intoxication and detoxication. Hepatic cytochrome P450 2E1 (CYP2E1) is proposed to be the main contributor to oxidative metabolism of TCE, although other P450s are also involved (Lash and Parker, (2001)[18]). Oxidative metabolism of PCE has also been attributed primarily to CYP2E1 activity owing to its structural similarity to other CYP2E1 substrates. The differences in metabolism here is due to the fate of the toxic intermediates from the metabolic pathway. TCE metabolites tend to induce more in end organ tissues including the kidneys.

In humans and experimental animals, the total flux of TVOCs through oxidative metabolism is thought to considerably exceed that through conjugative metabolism. However, as conjugative metabolites of TCE and PCE, they can form reactive metabolites that may rapidly bind to cellular macromolecules. Specifically, in the kidney, the conjugative pathway may more adversely affect the kidneys.

j. Conclusion: TVOC Exposure More Likely Than Not Causes Kidney Cancer.

The analysis of the Bradford Hill viewpoints demonstrates that TVOC exposure is causally linked to kidney cancer. Evidence supporting key viewpoints—including strength of association, consistency, dose-response, plausibility, and coherence—is strong.

In conclusion, there is significant epidemiological and mechanistic support in the literature supporting a causal relationship between TVOC exposure and the development of kidney cancer. Epidemiological studies strongly support a causal relationship. In particularly, Bove 2014a and 2014b support the causal relationship between TVOCs and kidney cancer. Finally, recent studies in animals and humans support that the TVOCs at issue and their metabolites cause DNA damage that leads to kidney cancer.

Applying the Bradford Hill viewpoints as described above, I conclude to a reasonable degree of scientific certainty that there is more likely than not a causal relationship between TVOC exposure and the development of kidney cancer. This conclusion exceeds the CLJA's "at least as likely as not" causation standard.

D. TCE and Kidney Cancer

1. TCE

Trichloroethylene (TCE) is chlorinated organic chemical that is a volatile and colorless liquid chemical. TCE was originally developed for use in hospitals as an anesthetic but it is now primarily used in refrigerants and in metal degreasing as a solvent to remove grease from metal surfaces. People can be exposed to TCE through indoor and outdoor inhalation, ingestion, or dermal exposure. TCE was frequently used by the U.S. military as an equipment degreaser, and thus, military bases have been found to have TCE-contaminated soil and groundwater. Soil degradation of TCE occurs very slowly and remains in the environment for a very long time.[12]

2. Systematic Reviews/Meta-Analyses

Kelsh et. al. (2010)[19] performed a meta-analysis of epidemiologic studies of occupational TCE exposure and kidney cancer. The authors identified 23 cohort and case-control studies that examined a TCE-exposed study population and determined relative risk estimates for kidney cancer. The studies included aerospace workers, workers from a transformer manufacturing plant and workers from numerous occupations who, based on biomonitoring or extensive industrial hygiene exposure measurements, were likely exposed to TCE. The RR estimate was 1.42 (95% CI: 1.17–1.77 with heterogeneity present at p=001). After removal of 3 outlier studies, the summary risk estimate was 1.24 (95% CI:1.06-1.45). While positive associations were observed, the study could be limited by potential confounding factors, no exposure measurements, and lack of an exposure-response relationship.

Scott CS. et. al. (2011)[20] conducted a meta-analysis and systematic review of workers with a high potential for TCE exposure to assess the risk of association between TCE and various cancers. In the analysis of kidney cancer risk, the authors found that TCE exposure increased the risk of kidney cancer and the risk ratio was elevated from the random effects model at 1.27 (95% CI: 1.13, 1.43). The risk was even higher for the highest exposure group with a risk ratio of 1.58 (95% CI: 1.28, 1.96). There was low misclassification bias; exposure classification accounted for exposure to other solvents and the studies included lacked exposure measurements but used biomarkers as indicators of exposure.

Karami et al (2012)[21] performed a systematic review and meta-analysis of TCE and kidney cancer risk. The authors reviewed 15 cohort, and 13 case control studies published between 1950 and 2011 that assessed only TCE exposure and kidney cancer risk. Their results revealed significantly elevated summary estimates for TCE exposures being associated with an increased risk of kidney cancer as noted in the summary risk estimate of 1.32 (1.17, 1.50).

3. Cohort Studies

Most of the cohort studies listed below have SMRs/RRs that are above the null in the 1.2 to 1.8 range. Studies with SMRs/RRs above 1.1 meets my definition of equipoise and above. This is also the threshold used by ATSDR in their determinations of what epidemiological studies were significant in their 2017 Assessment of the Evidence.

Anttila et. al. (1995) [22] conducted a retrospective cohort study of exposure to trichloroethylene, and tetrachloroethylene, and increased carcinogenic risk. The study followed a cohort of 2050 male and 1924 female workers monitored for occupational exposure to TCE that was followed up for cancer incidence from 1967 to 1992. The cancer incidence within the cohort had comparable results to that of the Finnish population. There was no excess risk of kidney cancer with a risk ratio of 0.95 (95% CI: 0.4-2.5). The study relied on biomarker monitoring for TCE exposure, so the risk of misclassification bias was low. The Antitila study showed risk that was close to equipoise and there was a wide confidence interval due to small numbers of cancer cases in the exposed cohort that resulted in a less precise risk estimate.

Raaschou-Nielsen O. et. al. (2003)[23] assessed cancer incidence between 1968 and 1997 in a cohort of 40,049 blue-collar workers in 347 Danish companies with documented trichloroethylene use. Standardized incidence ratios for total cancer were 1.1 (95% (CI): 1.04, 1.12) in men and 1.2 (95% CI: 1.14, 1.33) in women. For renal cell carcinoma, the overall standardized incidence ratio was 1.2 (95% CI: 0.9, 1.5). When duration of exposure was considered, the risk ratio progressively increased for both men and women with exposure < 1 year having a risk ratio of 0.8 (95% CI:0.5-1.4), 1 - 4.9 years had a risk ratio of 1.2 (95% CI: 0.8-1.7) and > 5 years had a risk ratio of 1.6 (95% CI 1.1-2.3).

Zhao Y, et al. (2005)[24] conducted a retrospective cohort study of 6107 aerospace workers employed at a California company between 1950 and 1993. High levels of TCE exposure were causally associated with kidney cancer incidence with a risk ratio of 4.90 and a significant 95% CI (1.23–19.6). Zhao also noted the risk increased with cumulative exposure going from risk ratio of 1.9 (95% CI: 0.6-5.2) at medium exposure to 4.9 (05%CI: 1.2 -19.6) at high exposure.

Radican L, et al. (2008)[25] performed a cohort study of TCE exposure and kidney cancer outcomes. TCE exposure was evaluated among aircraft maintenance workers. The cancer incidence follow-up was done for 18 years, from 1973-1990. Cancer mortality follow-up was performed for 48 years from 1953-2000. A job exposure matrix for TCE exposure was developed using industrial hygiene records. Kidney cancer relative risk was elevated, and the risk ratio was 1.9 for cumulative exposure of from 1-5 years. The risk ratio was 0.3 for 5 -25 years and the risk ratio over 25 years was 1.2 (95% CI: 0.3-4.3). The exposure intensity ranged from a low intermittent risk ratio of 1.6 (95% CI: 0.5-4.8) to low continuous of 1.8 (95% CI: 0.6-5.6). The peak infrequent exposures risk ratio was 1.0 (95% CI:0.2-5.7) and peak frequent exposures had a risk ratio of 1.1 (95% CI: 0.3-4.0). The Radican study noted a significant increased risk of kidney cancer in the cohort consistent with other cohort studies noted above.

Lipworth L, et al. (2011)[26] assessed TCE exposure and kidney cancer risk among aircraft manufacturing workers in a follow-up study between 1960 to 2008. A job exposure matrix was

developed for TCE using surveys and industrial hygiene records. The study authors found a relative risk of 0.84 (95% CI:0.48-1.47) for less than a year of TCE exposure and an elevated risk ratio of 1.1 (95% CI: 0.59-2.04) for 1 - 4 years of exposure. The risk ratio was only sightly elevated at 1.02 (95%CI: 0.55-1.50) for over 5 years of exposure.

Hansen J, et al. (2013)[27] performed a cohort study of TCE exposure among 5553 workers from companies in Finland, Sweden, and Denmark. Cancer incidence follow-up was done for 30 years, from 1968-1996. Urinary biomonitoring (U-TCA) measurements were used to assign TCE exposure. The overall risk for kidney cancer was noted to be an SIR of 1.01 (95% CI: 0.7-1.42). The authors also examined risk based on urinary TCA levels. Levels below 5 were considered controls. Between 5 and 25, there was an elevated risk ratio of 1.1 (95% CI:0.5-2.7). Between 25 and 50, the risk ratio was 0.8 (95% CI was 0.2-3.0), and for levels > 50 mg/L, the risk ratio was 2.0 (95% CI: 0.8-5.2). So, in my opinion, the risk ratio of 2.0 noted in the Hansen study for highest TCA levels reaches the level of equipoise and above for TCE exposure and kidney cancer.

Silver SR. et. al. (2014)[28] examined health outcomes among 34,494 workers employed at a microelectronics and business machine facility from 1969-2001. Approximately seventeen percent of the cohort (5,966 people) had died through 2009. Cumulative 5 exposure-year had an elevated hazard ratio of 1.24 (95%CI: 0.87-1.77).

Buhagen M, et. al. (2016)[29] examined the association between kidney cancer and TCE occupational exposure. The cancer incidence was examined in a cohort of 997 male workers who were exposed to TCE. The authors noted an increased standardized incidence ratio of 1.7 (95% CI: 1.0-3.0).

Boice et. al. (2006)[30] performed a retrospective cohort mortality study of persons working with nuclear technology development for at least 6 months at Rocketdyne (Atomics International) facilities in California, from 1948–1999. Expected numbers of deaths were computed based on race, age, calendar year and gender specific mortality rates in California. Kidney cancer was elevated with an SMR of 1.39 (95% CI: 0.56–2.86).

4. Case Control Studies

Pesch B et al. (2000)[31] conducted a population-based case-control study that was conducted to examine urothelial cancer risk due to occupational exposure to TCE and PCE exposure. There were 1035 incident urothelial cancer cases and 4298 controls matched for region, sex, and age between 1991 and 1995. The cumulative exposure in percentiles for the 30th, 60th, and 90th percentiles were examined. The results show an elevated risk ratio at 30th percentile of 1.3 (95% CI:1.0-1.8); there was an elevated risk at the 60th percentile of 1.1 (95% CI 0.8-1.5) and there was an increased risk ratio of 1.3 (95% CI: 0.8-2.1) at the 90th percentile of cumulative exposure for men. The risk at the 90th percentile was higher for women with the risk ratio of 1.8 (95%CI: 0.6-5.0).

Charbotel et. al. (2006)[32] performed a case-control study in the Arve Valley (France) to examine the association between TCE and renal cell cancer. There were 86 cases and 316 controls

matched for age and gender. The analytic approach used 3 categories 1) exposure for job period - one year minimum, 2) cumulative dose (TCE ppm per job period X number of years in the job period) and 3) peak exposure. The results show a significant increased risk of kidney cancer in the high cumulative doses with an odds ratio of 2.16 (95% CI:1.02-4.60). An exposure-response relationship was identified for cumulative exposure and for peak effect. The adjusted odds ratio for highest class of exposure-plus-peak being 2.73 (1.06-7.07). After adjusting for exposure to cutting fluids, the odds ratio for RCC in the highest cumulative TCE exposure was reduced to 1.96 (0.71–5.37). This study supports an equipoise and above risk of TCE and renal cell carcinoma.

Moore et. al. (2010)[33] conducted a case-control study in Europe with 1,097 cases and 1,476 controls specifically designed to assess risk for exposure to TCE using detailed job histories. The authors observed an increased risk of kidney cancer in TCE exposed with a risk ratio of 1.63 (95% CI: 1.04–2.54). The authors defined the risk of kidney cancer for varying levels of TCE exposure. For workers exposed to an average-intensity of exposure of less than 0.076 ppm (76 ppb), the relative risk of kidney cancer was 1.38, meaning a 38% increased risk. For workers exposed to more than .076 ppm (76 ppb), the relative risk of kidney cancer was 2.34, (a 134% increased risk). As detailed above, these concentrations of TCE are comparable to those observed at Camp Lejeune—particularly at Hadnot Point, where TCE levels were in the hundreds of parts per billion.

The authors also conducted an analysis of kidney cancer risk based on cumulative risk of TCE exposure. For workers who had less than 1.58 ppm-years of exposure, the relative risk of kidney cancer was 1.19, equivalent to a 19% increased risk of kidney cancer. For workers who had between 0 and 1.58 ppm-years of exposure, the relative risk of kidney cancer was 2.02, equivalent to a 102% increased risk, again more than a doubling of the risk. They also observed an exposure-response trend moving from low, to medium and above exposure with an elevated risk ratio of 1.38 (95% CI: 0.81–2.35) going to a risk ratio 2.34 (95% CI: 1.05–5.21) P trend = 0.02) for medium-high category.

The authors linked TCE exposure and genotype testing for changes in the GSTT1 enzyme pathway. People who had one intact GSTT1 allele had an elevated risks for kidney cancer. The findings of this study agree with and support the hypothesized mechanism for TCE-induced kidney cancer and therefore provide strong evidence for causality of TCE and kidney cancer.

Vlaanderen et al. (2013)[34] noted the risk ratio for any exposure was 1.00 (95% CI: 0.95-1.07) and the risk ratio for >90% cumulative exposure was 0.86 (95%CI: 0.75-0.98) so the authors did not observe an increased risk for kidney cancer. The authors used a generic JEM that was likely to introduce considerable exposure misclassification bias. Further, few people were in the high exposure group for either TCE or PCE.

Christensen et al. (2013)[35] noted the risk ratio for any exposure was 1.00 (95% CI: 0.3-2.9) and the risk ratio for >90% cumulative exposure was 0.70 (95%CI: 0.01-3.20) so the authors did not observe an increased risk for kidney cancer. There were some limitations in that the study had very few exposed cases.

Blair A. et. al. (2003)[36] conducted a cohort study of workers in dry cleaning that was extended to further evaluate cancers risks associated with organic solvents. The cohort was 5,369 members of a dry-cleaning union in St. Louis, MO from 1960 to December 31, 1993. The mortality of the cohort was compared to the US population and adjusted for age, year of death, race and gender. The total mortality SMR was 1.0 for kidney cancer. A causal association was observed for kidney cancer among black men and women. There was an increased risk of death from kidney cancer in people who had medium/high levels of exposure with an SMR of 1.5 (95% CI: 0.6-3.1). The authors wrote that the excesses observed are unlikely to be due to chance. The risk estimate was less precise due to the small numbers of cases.

Purdue et. al. (2017)[38] investigated kidney cancer associations with occupational exposure to 6 solvents trichloroethylene, perchloroethylene, and 4 others within a case–control study using detailed exposure assessment methods for 1217 cases and 1235 controls. For jobs with high exposure and high cumulative hours of exposure, PCE was associated with increased risk of kidney cancer (third tertile vs unexposed: OR 3.1, 95% CI 1.3 to 7.4). After taking out participants with greater than or equal to 50% exposure probability for TCE the OR were elevated still (OR 3.0, 95% CI 0.99 to 9.0). A causal relationship with high cumulative hours of exposure to TCE was also observed (OR 1.7, 95% CI 0.8 to 3.8).

These studies provide significant and robust evidence that TCE can cause kidney cancer. Although the concentrations involved in some of these studies was higher than the monthly mean concentrations present at CLJ, these studies should not be interpreted to mean that lower levels of exposure do not cause kidney cancer. The studies only dealt with the levels of exposure at issue in their particular set of circumstances and therefore could not have dealt with lower levels. Instead, these studies simply confirm with great certainty that the levels of exposure present in the occupational studies are enough to cause kidney cancer.

5. Water Contamination Studies

New Hampshire:
Andrew A. et. al. (2022)[40] conducted a community population health study that included a detailed spatiotemporal analysis of estimated residential TCE exposure in New Hampshire, US. They identified 292 kidney cancer cases and selected 488 controls with age and gender matching from the Dartmouth-Hitchcock Health System. They used publicly available data on TCE levels in groundwater at contaminated sites in New Hampshire and modeled the spatial dispersion. They overlaid geospatial residential locations for cases and controls with yearly maps of estimated TCE levels to estimate median exposures over the 5, 10, and 15-year time periods before diagnosis. Although the amount of contamination in the water varied, the median level was 135 micrograms per liter, equivalent to 135 ppb. This is comparable to the levels of TCE concentration modeled at Camp Lejeune, in particular Hadnot Point, where TCE levels often ranged in the hundreds and maxed out at more than 1,000 micrograms per liter. The 50th–75th percentile of estimated residential exposure over a 15-year period was associated with increased kidney cancer risk that had an adjusted Odds Ratio of 1.78 (95% CI 1.05–3.03), compared to individuals who were exposed below the 50th percentile. These findings support that elevated TCE levels in the drinking water in New Hampshire were sufficient to cause kidney cancer and these levels were similar to those found in the drinking water at Camp Lejeune.

Woburn, Massachusetts:

Parker and Rosen (1981),[41] Massachusetts Department of Public Health conducted a cancer mortality study and observed a significantly higher cancer mortality rate in Woburn compared to state averages and nearby communities for kidney cancer. The expected number of incident cases for kidney cancer was calculated using age and sex-specific incidence data from the Third National Cancer Survey (TNCS). The incidence of renal cancer in Woburn was significantly elevated for the period 1969 – 1978. Thirty cases were observed whereas 19.4 were expected $p < .05$. Cuttler (1986)[42] documented the TCE levels in the contaminated public water supply wells G and H for TCE were 267 ppb and for PCE were 21 ppb. These contaminant levels are comparable to those at Camp Lejeune. The study underscores the hazardous nature of the chemicals present in Woburn's water, showing that TCE and PCE exposure levels were sufficient to cause kidney cancer. It also reinforces the conclusion that the TCE and PCE levels at Camp Lejeune also posed significant risks to human health and supports the findings of increased kidney cancer risk at Camp Lejeune.

Alanee et. al. (2015)[43] conducted an analysis of the kidney-cancer mortality in counties with drinking water contamination with varying levels of TCE discharge. The authors found that "compared to counties with low release, counties with intermediate and high TCE release had higher average mortality rates for kidney cancer." Although the authors did not detect "an association between TCE exposure and kidney cancer incidence," they did demonstrate that "high TCE releases are associated with increased kidney cancer mortality at the county level." They also showed "a dose-response relationship between TCE exposure and mortality from kidney cancer." Despite the limitations, this study provides additional support for the association between TCE exposure and kidney cancer even at concentration levels far lower than those present in the occupational studies and comparable to the levels at Camp Lejeune.

6. International Agency Reports / National Toxicology Program

The International Agency for Research on Cancer (IARC), the cancer research arm of the World Health Organization, is a vital resource for scientists and experts. IARC monographs and carcinogen classifications are widely used in research to assess the carcinogenicity of various agents. IARC categorizes agents into four groups: Group 1 ("carcinogenic to humans"), Group 2A ("probably carcinogenic to humans"), Group 2B ("possibly carcinogenic to humans"), and Group 3 ("not classifiable as to its carcinogenicity to humans").

IARC (2014)[16] Monograph 106 specifically addressed TCE and evaluated its carcinogenicity. The IARC Working Groups base their classifications on human epidemiological evidence, animal evidence, and mechanistic data. TCE was classified as Group 1 carcinogen, meaning it is "carcinogenic to humans." In Monograph 106, the IARC Working Group made the following key determinations regarding TCE:

- Human evidence related to TCE's carcinogenicity was classified as "sufficient," the highest level of evidence under IARC's framework.
- Animal evidence related to TCE's carcinogenicity was also classified as "sufficient."
- TCE metabolites were identified as genotoxic.

- TCE was found to be immunotoxic.

Overall, IARC (2014)[16] concluded the epidemiological evidence for kidney cancer is sufficient to establish a causal relationship between TCE exposure and kidney cancer.

NTP (2015)[14] stated in its assessment that "the increased risks found across the epidemiological studies were unlikely to be explained by biases. IARC (2014)[16] and EPA (2011)[12] have determined that there is sufficient evidence in humans that TCE causes kidney cancer". NTP (2015)[14] noted that increased risks were observed in studies with higher levels of exposure and better exposure assessments. The NTP[44,45] concluded: "Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk across studies with different study designs, in different geographical areas, and in different settings; evidence of increasing cancer risk with increasing level or duration of exposure; and meta-analyses showing statistically significantly increased cancer risk across studies." The NTP highlighted the strongest epidemiological evidence for kidney cancer in meta-analysis by studies by Kelsh,[19] Scott,[20] and Karami.[21] These studies provided positive associations between TCE exposure and kidney cancer.

7. Animal Study Evidence for an Association between TCE and Kidney Cancer

The National Toxicology Program, (2015, 2021)[44-46] 15th Report on Carcinogens (ROC) indicated that Trichloroethylene was noted to cause increased liver cancer in mice. Trichloroethylene was administered to rats by breathing inhaled vapors and was administered into the stomach via nasovascular and this lifetime exposure caused cancer in the affected male rats. In mice, breathing trichloroethylene or injecting TCEs into the stomach caused benign and malignant liver tumors in both sexes.[44] The National Toxicology Program Monograph on Trichloroethylene (2015 p. 106)[14] also reported exposure to TCE via inhalation or stomach tube caused kidney cancer in rats. Trichloroethylene caused testicular cancer and leukemia in rats and lymphomas and lung tumors in mice. It is my opinion that the animal studies do provide evidence of an association between TCE exposure and increased kidney cancer risk.

8. Mechanistic Evidence of an Association between TCE and Kidney Cancer

It is my opinion that the mechanistic studies on TCE (both in humans and animals, and in vitro) demonstrate that TCE causes an increased risk for kidney cancer. TCE can be metabolized through both an oxidative and reductive pathway. Trichloroethylene works to cause kidney cancer by causing mutagenic and cytotoxic changes that are predominantly caused by GSH-conjugation-derived metabolites or breakdown products of trichloroethylene. The TCE interacts with the genes that turn on GSTT1 and renal-CCBL enzymes. Once the enzymes are active in the kidney, they cause bioactivation of TCE through GSH-conjugation and the end products of the metabolism cause genotoxic and nephrotoxic effects.

Moore (2010)[33] examined the metabolic pathway for TCE and documented genotype changes in the GSTT1 enzyme pathway and observed that people who had one intact GSTT1 allele had an elevated risk for kidney cancer. Other people with two alleles were not at increased risk for kidney cancer. These study findings provide strong support for the hypothesized mechanism of action discussed above for TCE exposure causing kidney cancer and therefore provide strong evidence for causality of TCE and kidney cancer.

Toxicology studies in animals also note that TCE causes kidney damage after bioactivation through the reductive metabolic pathway. This requires prior hepatic and renal glutathione S-transferase (GSH) conjugation and subsequent cleavage by renal cysteine conjugate β-lyase to form cysteine S-conjugates; S-(1,2,dichlorovinyl-L-cytseine) and S-(1,2,2-trichlorovinyl L-cysteine) Moore (2010).[33] These metabolites are highly reactive and cause formation of DNA-adducts, strand breaks, bacterial mutagenicity, and renal cell genetic damage and cell injury and death. Moore examined the reductive pathway to see if changes in common genes involved in reductive metabolism would modify TCE-associated renal cell carcinoma risk. The enzyme GSTT1 catelyzes the conjugation of small, halogenated compounds like TCE. In addition, the renal CCBL1 gene was selected because there are no known functional polymorphisms identified that directly affect enzyme activity or expression. Moore et. al.(2010)[33] observed that a single allele deletion was necessary to cause the genetic mutation that could lead to carcinogenicity.

9. Applying the Bradford Hill Viewpoints in this Case

Having reviewed the evidence regarding the association between TCE and kidney cancer, it is useful to assess this evidence according to the Bradford Hill viewpoints. It is not possible to reproduce all of the above evidence in each viewpoint, but summaries of the evidence will be provided below.

a. Strength of association

This viewpoint is met in this case because several meta-analyses as well as cohort and case control studies provide consistent evidence supporting a strong association between TCE exposure and kidney cancer. Kelsh et. al. (2010),[19] Scott CS.et. al.(2011)[20] and Karami et al (2012)[21] conducted meta-analyses of occupational TCE exposure and kidney cancer and noted strong evidence of a causal association between TCE and kidney cancer. Furthermore, several cohort studies provided additional support for the association. Raaschou-Nielsen O. et. al. (2003)[23] assessed cancer incidence in a cohort of 40,049 workers in 347 Danish companies with TCE documented use. They noted SIRs for renal cell carcinoma of 1.2 (95% CI: 0.9, 1.5) and documented a progressive increase in risk ratio for each exposure level < 1 year with a risk ratio of 0.8 (95% CI:0.5-1.4), 1-5 years had a risk ratio of 1.2 (95% CI: 0.8-1.7) and > 5 years had a risk ratio of 1.6 (95% CI 1.1-2.3). Zhao Y, et al. (2005)[24] conducted a retrospective cohort study of 6107 aerospace workers to assess exposure TCE and benzene. High levels of TCE exposure levels were positively associated with kidney cancer incidence of 4.90 (95% CI (1.23–19.6). Zhao also noted an exposure response relationship for cumulative exposure going from risk ratio of 1.9 (95%CI: 0.6-5.2) at medium exposure to 4.9 (05%CI: 1.2 -19.6) at high exposure.

Hansen J, et al. (2013)[27] performed a cohort study of TCE exposure among 5553 workers from companies in Finland, Sweden, and Denmark with follow-up from 1968-1996. Urinary biomonitoring (TCA) measurements were used to assign TCE exposure. The overall risk ratio for kidney cancer was noted to be 1.01 (95% CI: 0.7-1.42). The authors examined risk based on urinary TCA levels. Levels below 5 were controls. Between 5 and 25, there was an elevated risk ratio of 1.1 (95% CI:0.5-2.7), between 25 and 50, the risk ratio was 0.8 (95% CI was 0.2-3.0), and for levels > 50 mg/L, the risk ratio was 2.0 (95% CI: 0.8-5.2). So, the highest TCE levels had a risk ratio of 2.0 which is considered above equipoise for kidney cancer. Silver SR. et. al. (2014)[28] examined health outcomes among 34,494 workers employed at a microelectronics facility from 1969-2001. Cumulative 5 exposure-year had an elevated hazard ratio of 1.24 (95%CI: 0.87-1.77). Buhagen M, et. al. (2016)[29] examined the association between TCE and kidney cancer and noted an increased SIR of 1.7 (95% CI: 1.0-3.0).

Drinking water studies also contributed to the strength of the evidence for an association between TCE and kidney cancer.

As discussed above, Bove et. al. 2014a[5] found that compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), and the risk for kidney cancer was elevated with an SMR of 1.35 (95% CI: 0.84, 2.16). There were monotonic responses for cumulative exposure to total volatile organic contaminants (TVOCs) and kidney cancer with a RR for high cumulative exposure of 1.54 (95% CI: 0.63, 3.75) $\log_{10}$ β =0.06, 95% CI:-0.05, 0.17).

Further, Bove 2014a[5] analyzed cumulative exposure to TCE and found that there were HR of 1.54 (low exposure), 1.21 (medium exposure) and 1.52 (high exposure).

The ATSDR (2017)[2] report concluded that the epidemiological evidence for TCE and kidney cancer from meta-analyses, cohort, and case control studies was above equipoise.

The Bove (2024)[9] cancer incidence study on Camp Lejeune personnel indicated that compared with Camp Pendleton, Camp Lejeune Marines/Navy personnel had an elevated SIR of 1.12 (95% CI: 0.76-1.67) for RCC for civilians.

Thus, in my opinion, the evidence supports the association reaching an as likely as not or equipoise and above standard for the risk of kidney cancer following TCE exposure.

b. Consistency

The consistency viewpoint is supported by findings across multiple meta-analyses, cohort and case control studies. This consistency in findings across various study designs supports the causal relationship between TCE and kidney cancer, as detailed above.

c. Specificity

The specificity viewpoint limited in this case because there are many different diseases that are caused by TCE. However, because epidemiological evidence demonstrates a clear and specific

association between TCE exposure and kidney cancer, distinguishing it from other exposures and outcomes, it provides some limited evidence.

While TCE exposure may also be associated with other diseases, the evidence presented here consistently shows that kidney cancer is more strongly linked to TCE exposure compared to other outcomes. This level of specificity in the population, the chemical exposure, and the disease provides some limited support for the causal inference between TCE and kidney cancer.

d. Temporality

The temporality viewpoint is unequivocally satisfied in this case, as all studies demonstrating an association between TCE exposure and kidney cancer confirm that the exposure occurred prior to the onset of disease. This criterion is foundational to causal inference because, as Bradford Hill emphasized, the cause must precede the effect.

e. Exposure-Response

As noted in the three systematic reviews and meta-analyses, several studies demonstrated an exposure response relationship with kidney cancer risk. In my opinion, the evidence in support of this criterion is present, and strong.

f. Biological Plausibility

As discussed above, TCE's genotoxicity and its ability to induce epigenetic modifications strongly support biological plausibility. Animal studies demonstrate that TCE and its metabolites cause metabolism disruption, activation of pathway intermediates and development of genetic damage that leads to kidney cancer development. Thus, the noted mechanistic alterations strengthen the biological plausibility of TCE as a cause of kidney cancer, that complements the results from the epidemiological findings. Thus, it is my opinion the evidence for this criterion is strong.

g. Coherence

The coherence criterion evaluates whether epidemiological findings align with biological and toxicological knowledge. Studies consistently show an association between TCE exposure and kidney cancer. Mechanistic and animal studies confirm that TCE's genotoxicity and genetic changes align with these increased kidney cancer risks. Both IARC and NTP have noted this alignment, reinforcing the coherence between the evidence and causal inference.

h. Experimental Evidence

While human experimental evidence is unethical to obtain, animal studies robustly demonstrate that TCE induces genotoxic effects. Further, the epidemiological studies that have been done based on exposures already existing support a causal relationship between TCE and kidney cancer. This supports the role of TCE in carcinogenesis.

i. Analogy

Metabolic pathways of TCE and PCE are similar. Major metabolites of TCE and PCE include the cytochrome P450-mediated oxidation and GSH conjugation. The metabolites include oxalate; trichloroacetyl chloride; and trichloroethanol O-glucuronide. Cichocki JA, et. al. (2016).[17a]

TCE and PCE have qualitatively similar metabolic schemes in rodents and humans (IARC, 2014[16]). Metabolism of TCE and PCE can result in both intoxication and detoxication. Hepatic cytochrome P450 2E1 (CYP2E1) is proposed to be the main contributor to oxidative metabolism of TCE, although other P450s are also involved Lash and Parker, (2001).[18] Oxidative metabolism of PCE has also been attributed primarily to CYP2E1 activity owing to its structural similarity to other CYP2E1 substrates. The differences in metabolism here is due to the fate of the toxic intermediates from the metabolic pathway. TCE metabolites tend to induce more in end organ tissues including the kidneys.

In humans and experimental animals, the total flux of TCE and PCE through oxidative metabolism is thought to considerably exceed that through conjugative metabolism. For TCE, major metabolites are TCOH and TCA; for PCE, TCA is the major metabolite. In both humans and experimental animals, it is evident that exposure to TCE or PCE results in larger urinary levels of oxidative TCE/PCE metabolites compared with mercapturic acids derived from the GSH conjugation pathway. However, as conjugative metabolites of TCE and PCE, they can form reactive metabolites that may rapidly bind to cellular macromolecules. Specifically in the kidney, the conjugative pathway may more adversely affect the kidneys.

The analysis of the Bradford Hill viewpoints demonstrates that TCE exposure is causally linked to kidney cancer. Evidence supporting key viewpoints—including strength of association, consistency, dose-response, plausibility, and coherence—is strong.

10. Conclusion: TCE Exposure More Likely Than Not Causes Kidney Cancer

In conclusion, there is substantial epidemiological and mechanistic support in the literature for a causal relationship between TCE exposure and the development of kidney cancer. Epidemiological studies strongly support a causal relationship. In particularly, findings from Kelsh et. al. (2010),[19] Scott CS.et. al.(2011),[20] and Karami et al (2012),[21] ATSDR's (2017)[2], Bove (2014)[5,6] and Bove (2024)[8,9] studies support the causal relationship between TCE and kidney cancer. Finally, recent studies in animals and humans support that TCE and its metabolites cause DNA damage that leads to kidney cancer. Applying the Bradford Hill viewpoints, I conclude, to a reasonable degree of scientific certainty, there is more likely than not a causal relationship between TCE exposure and the development of kidney cancer. This conclusion exceeds the CLJA's "at least as likely as not" causation standard, as described above.

E. Benzene and Kidney Cancer

1. Benzene Generally

Benzene is an aromatic hydrocarbon. It is an air pollutant and comes mostly from anthropogenic sources, including combustion. It is a part of gasoline, vehicle exhaust, industrial emissions, and tobacco smoke, and has been used as a solvent in industry and consumer products. The uses of benzene as a solvent are now restricted in many countries, but it is still produced in high volumes for use primarily as a chemical intermediate. Occupational exposure to benzene can occur in diverse industries, including petroleum, chemical production, and manufacturing. People can be exposed to benzene in polluted air and water, as well as through the use of benzene-containing products. The IARC Working Group on Benzene (2018)[49-50] noted concentrations less than 3.00 and 0.005 mg/m3 in workplace and outdoor air, respectively, in high-income countries, but higher levels have been reported in some low-income and middle-income countries.

2. IARC's Assessment of Benzene

a. Carcinogenicity Assessment

Benzene has been classified as carcinogenic to humans (IARC Group 1) in IARC Monographs Volume 100F,[49] based on sufficient evidence that it causes cancer. The evidence available on the association between occupational exposure to benzene and cancer of the kidney was reviewed in IARC Monographs Volume 100F,[49] and judged to be inadequate at that time.

b. Kidney Cancer Risk Assessment

The pertinent occupational cohort studies were reviewed in IARC (2012)[49] Volume 100F and IARC (2018)[50] Monograph Volume 120 on Benzene and The Evaluation of Carcinogenic Risks To Humans still notes that there is insufficient evidence for benzene exposure causing kidney cancer. The studies generally do not conclude a pattern of association, although several studies did report elevated but not statistically significant risks for cancer of the kidneys. Seyyedsalehi et. al. (2024),[51] Tsai et al., (1993),[52] (Sorahan et al., 2005)[53] and Bulbulyan et al. (1999)[54] demonstrate some increased risk

3. Systematic Reviews and Meta-Analyses

Seyyedsalehi et. al. (2024)[51] examined occupational benzene exposure and risk of kidney cancer in a systematic review and meta-analysis that included 41 studies including 33 cohort and 8 case-control studies including all studies that were reported in the IARC 2018 Monograph on benzene exposure. Relative risks were plotted for kidney and urinary tract cancer. A random-effects model was used to address heterogeneity between studies. Stratified analyses were conducted to explore effect modification. There was a causal relationship between benzene exposure and kidney and unspecified urinary tract cancers (RR = 1.20, 95% confidence interval = 1.03-1.39). This recent systematic review and meta-analysis provides strong evidence of an association between benzene exposure and kidney cancer.

4. Cohort Studies

Tsai et al., (1993)[52] examined the mortality experience of 4221 employees from 1973 to 1999 for Mortality. Illness absence data was extracted from the Shell Oil Company's health surveillance system (HSS). The standardised mortality ratio for kidney cancer was elevated with 6 deaths observed and 4.6 expected. That yielded an SMR of 1.31 (95% CI: 0.48-2.85).

Sorahan et al., 2005[53] examined mortality from different causes and cancer incidence among a cohort of 5514 workers who had been occupationally exposed to benzene in 1966/67 in England and Wales. National mortality rates and cancer registration (incidence) rates were used to calculate standardised mortality ratios for the cohort. The authors noted there was slightly above equipoise Kidney cancer risk with an SMR of 103 (95% CI: 56 to173). The authors note there was some misclassification bias possible with the way exposure ascertainment was performed so this would lower the SMR towards the null.

Bulbulyan et al. (1999)[54] performed a cancer mortality study of 3473 women employed in two large printing plants in Moscow. The authors used the population of Moscow to generate expected case numbers for the SMR analysis. They reported a standardized mortality ratio of 1.4 (95% CI:0.5-3.1) for the whole plant and 1.9 (95% CI, 0.4–5.6; n = 3) among bookbinders who were primarily exposed to benzene.

Wong (1987a, b)[55] reported on a nested case–control study of United States of land and marine petroleum distribution workers who were exposed to gasoline containing 2–3% benzene. The study looked at duration of exposure, cumulative exposure, and frequency of peak exposure. The overall SMR for the cohort was 0.85 (95% CI, 0.27–1.98; n = 5). The authors did find an excess mortality risk due to kidney cancer with an SMR of 1.49 for workers who were in the 10-19 year exposure category. The SMR for workers with longer cumulative exposures was below 100. The authors felt that exposure misclassification and a “healthy worker effect” were possible to be found in the analysis results.

Collins et al. (2015)[56] found no excess mortality from kidney cancer with a low SMR of 0.78 (95% CI: 0.34–1.55). Collins et al., (2015)[56] followed upon and updated the Dow Chemical workers, Midland, Michigan cohort mortality study of 2,266 workers exposed to benzene. Data was derived from the company’s research database. The database sourced from different locations, including the National Death Index. The follow-up, starting in 1940, was extended by 13 years to the end of 2009. Measurements of benzene were used to estimate exposures. The average exposure duration was 4.9 years (range, 30 days–44.7 years). Exposures were divided into three categories (0–3.9, 4.0–24.9, and ≥25 ppm-years).

5. Case Control Studies

Pesch et al., (2000)[57] conducted a study of 935 incident cases and 4298 controls interviewed between 1991 and 1995, with exposure estimated according to occupational history and a JEM. The results indicated that employment durations exceeding the 90th percentile in the chemical, rubber, and printing industries were associated with urothelial cancer/renal cell carcinoma. Substantial exposure to benzene in the exposed British and German groups of workers with

medium, high, and substantial exposures had elevated risk ratios of 1.1 (95% CI:0.8-1.4), 0.9 (95% CI: 0.7-1,2), and 1.5 (95% CI: 1.0-2.1). Thus, benzene exposure increased the risk of urothelial cancer in workers with exposure at all levels in both men and women.

Gérin et al., (1998)[58] conducted a population-based case-control study carried out in Montreal, Canada. There were 3,730 cancer patients and 553 controls. Exposures were estimated using interviews and a team of experts. Benzene exposure levels were low for most exposed subjects. There was a 30% increased risk of an association between medium and high levels of benzene exposure and kidney cancer with a risk ratio of 1.3 (95% CI, 0.7–2.4).

Greenland et. al. (1994)[59] conducted a proportionate mortality study to examine excess cancer mortality in a large transformer manufacturing plant, with exposures to PCB, trichlorobenzene; trichloroethylene, and benzene. Site-specific cancer deaths were calculated along with person-years of exposure. The kidney cancer risk was elevated with a risk ratio of 4.29 (95% CI: 1 33, 13 8), following adjustment for age, hire year, death year and age at death, the risk of kidney cancer was still elevated at 1.9 (95% CI:0.92-4.0). Study power was very limited and the authors recommended further investigation in the plant.

6. Animal Experiments

The IARC Working Group (2018)[50] determined that benzene is carcinogenic to humans based on evidence in humans and animals that is supported by mechanistic study data. The 2021 National Toxicology Program Assessment on Benzene[60] reported benzene is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans and laboratory animals. Animal studies of exposure to benzene caused tumors in multiple sites in rats and mice with lymphomas occurring in mice Huff et. al (1989).[61]

There is a lot of mechanistic evidence that details how benzene may cause bone marrow cancers. This occurs primarily through the genotoxicity of reactive metabolites of benzene that occurs in hematopoietic tissue progenitor cells, and liver. When benzene was injected by intraperitoneal injection, it caused benign lung tumors in male mice. When benzene was applied to the skin, it caused benign skin tumors in transgenic mice carrying the v-Ha-ras oncogene, which increased their susceptibility to carcinogens (Blanchard et al. (1998),[62] Spalding et al. (1999),[63] French et. al. (2001)).[64] In mice with only one functional copy of the p53 tumor-suppressor gene, benzene administered by stomach tube caused cancer of head and neck, thoracic cavity, and subcutaneous tissue, Hulla et al. (2001).[65] Multiple organs including the spleen, thymus, lymph node, kidney, lung, and/or brain were infiltrated with cancer cells.

7. Mechanistic Effects

Benzene is absorbed, distributed, and metabolized, to intermediate species that are reactive electrophiles that work via multiple metabolic pathways in various tissues, including bone marrow. It exhibits many of the key characteristics of carcinogens ATSDR 2024.[66] In humans, benzene is metabolically active, causes oxidative stress, is genotoxic, and is immunosuppressive. In addition, evidence from experimental studies shows that benzene causes genomic instability,

inhibits topoisomerase II, alters aryl hydrocarbon receptor binding and induces apoptosis. NTP (2021).[60]

Studies of carcinogenicity in mice exposed to benzene orally and by intraperitoneal injection caused a significant increase in epithelial hyperplasia, hyperplasia of the bone marrow, and lymphoma or leukemia (combined); alveolar epithelial hyperplasia, lung adenomas and carcinoma; hyperplasia and adenoma or carcinoma (combined) of the Harderian gland; epithelial hyperplasia, hyperkeratosis, and squamous cell papilloma of the forestomach.

Benzene primarily causes chromosomal aberrations that are frequently seen in peripheral blood lymphocytes and bone marrow. Benzene can enter the body through all pathways. In most of these studies, chromosome abnormalities were detected in workers exposed to high concentrations of benzene. ATSDR (2024)[66] Studies have found that benzene-exposed workers have high levels of epoxide and benzoquinone-protein adducts in the blood. Additionally, benzene causes oxidative stress in human cells, and mouse bone marrow. In studies of workers, benzene was noted to cause oxidative DNA damage, DNA strand breaks, gene mutations, and chromosomal aberrations. Specific cytogenetic changes include aneuploidy, translocations, and chromatid exchanges. Animal studies show similar findings in the bone marrow of experimental animals exposed in vivo. Benzene causes DNA adduct formation, and chromosomal aberrations. Similarly, in human cells in vitro, benzene or its metabolites cause DNA adducts to form and chromosomal aberrations. Benzene exposure causes toxicity in blood cell lines ranging from decreased white blood cell counts at lower exposures to aplastic anemia and pancytopenia at higher exposure levels ATSDR (2024).[66] The benzene-induced hematotoxic changes have been linked to leukemia and lymphoma in the future.

8. NTP's 2021 Assessment of Benzene

The National Toxicology Program (NTP) (2021)[60] functions as an interagency effort under the Public Health Service, part of the U.S. Department of Health and Human Services. It is housed within the National Institute of Environmental Health Sciences, a branch of the U.S. National Institutes of Health. The NTP is dedicated to researching, testing, and analyzing potentially hazardous substances to understand their toxicological and biological impacts. This work is vital for building a robust scientific foundation that informs health regulatory and research agencies in their efforts to safeguard public health.

When evaluating cancer risks, the NTP uses a thorough, step-by-step methodology based on established criteria. This approach incorporates evidence from human studies, animal experiments, and mechanistic research. Draft monographs are reviewed by external experts before being finalized and released. In my assessment, NTP monographs, similar to those from the International Agency for Research on Cancer (IARC), are regarded as highly credible and influential, with conclusions that hold significant authority. In 2015, the NTP released a monograph on benzene, which was subsequently updated in 2021 as part of its *Reports on Carcinogens.* During this review, the NTP applied systematic review methods to identify relevant studies, assess their quality, integrate findings across studies, and evaluate data from human, animal, and mechanistic sources.

Based on its evaluation, the NTP concluded that there is sufficient evidence to classify benzene as a human carcinogen. This determination was supported by epidemiological research, along with toxicological, toxicokinetic, and mechanistic studies that demonstrated the biological plausibility of benzene's carcinogenic effects in humans.

9. Recent Studies Published since the IARC and NTP Reports

DeMoulin, et. al. (2024)[67] investigated associations between occupational benzene exposure and kidney cancer risk in a population-based cohort of 61,377 men aged 40 to 74 years. The authors noted there was an increased risk of kidney cancer with an elevated risk ratio of 1.1 (95% CI: 0.8-1.5). The two exposure categories 1–198 mg/m3*years , and 199–550 mg/m3*years had elevated risk ratios of 1.3 (95% CI: 0.9-2.0) and 1.2 (95% CI: 0.7-2.0) respectively but the highest exposure category over 550 mg/m3*years was not elevated, and the risk ratio was 0.50 (95% CI: 0.2-1.3) for kidney cancer.

10. Bradford Hill Viewpoints

a. Strength of association

The strength of the association is supported by the meta-analysis by Seyyedsalehi et. al. (2024)[51] that examined occupational benzene exposure and risk of kidney cancer in 33 cohort and 8 case-control studies. This showed a significant link between benzene exposure and kidney cancer. The authors observed an association between benzene exposure and an elevated risk of kidney cancer with a risk ratio of 1.20 (95% CI: 1.03-1.39).

Bove 2014a[5] separately analyzed cumulative exposure to Benzene and found HR of 1.31 (low exposure), 1.38 (medium exposure) and 1.36 (high exposure). This supports this viewpoint.

The other studies that show this strength of association are listed above and provide significant evidence of a causal relationship between benzene and kidney cancer.

b. Consistency

As can be seen in the most recent meta-analysis by Seyyedsalehi et. al. (2024)[51] that examined occupational benzene exposure and risk of kidney cancer, there was a significant link between benzene exposure and kidney cancer. The authors observed an elevated risk of kidney cancer of 1.20 (95% CI: 1.03-1.39). Thus, the findings of the systematic review and meta-analysis demonstrate a statistically significant elevated risk of kidney cancer in relation to benzene exposure. In my view, this provides compelling evidence in support of this criterion.

c. Specificity

This viewpoint is hard to meet given that benzene has been linked with many other disease. However, the epidemiological evidence reviewed in this analysis specifically addresses the association between benzene and kidney cancer, focusing exclusively on studies where benzene exposure is clearly isolated from other exposures, and kidney cancer and its subtypes are

differentiated from other hematological malignancies. In my opinion, this provides limited support for this criterion.

d. Temporality

Studies examining benzene exposure and kidney cancer found a notable link. In those studies reviewed in the meta-analyses, exposure occurred before the onset of kidney cancer, thereby establishing a temporal relationship. In my view, there is substantial evidence backing up this criterion.

e. Dose-Response

Several studies, as detailed in the systematic review and meta-analysis conducted by Seyyedsalehi et. al. (2024),[51] showed evidence of an exposure-response relationship between benzene exposure and kidney cancer. The Hu study (2002) also found a monotonic response for benzene and kidney cancer. However, this evidence was not strong. In my opinion, the evidence in support of this criterion is present but weak.

f. Biological Plausibility

The human, mechanistic, and experimental evidence are supportive based on evidence of genotoxicity, and biomarkers consistent with cancer changes related to miRNA, epigenetics, and chromosomal damage and aberrations. This is described in detail in the sections above. Thus, in my opinion, the evidence in support of this criterion is strong.

g. Coherence

The correspondence between the epidemiological evidence and the experimental toxicological evidence noted by IARC and NTP, and confirmed by my review, is consistent with coherence.

h. Experimental Evidence

There is strong epidemiological evidence showing a causal relationship between benzene exposure and kidney cancer. However, conducting such research intentionally exposing individuals to benzene would be unethical. It's worth noting that the available toxicological evidence on benzene's genotoxic mechanisms stems from a body of well-conducted animal experiments. The body of epidemiologic literature showing the causal connection of benzene and kidney cancer is listed above and supports this consideration.

i. Analogy

There is similarity between the likely mechanisms of action of benzene with other genotoxic agents known to cause DNA damage that has led to kidney cancer. This supports this viewpoint. For example, there are similarities between the way that benzene, TCE, PCE and VC interact with the body and the mechanisms by which they cause kidney cancer.

11. Conclusion: Benzene Exposure As Likely As Not Causes Kidney Cancer

In conclusion, the epidemiological evidence of the association between benzene and cancer is sufficient. There is considerable epidemiological and mechanistic evidence available that benzene causes kidney cancer per the systematic review and meta-analyses conducted by Seyyedsalehi et. al. (2024)[51] observing an elevated risk of kidney cancer with a risk ratio of 1.20 (95% CI: 1.03-1.39). Bove (2014)[5,6], and Bove (2024)[8,9], as well as recent studies of benzene's genotoxicity and chromosomal aberrations, are also supportive of a causal relationship between benzene and kidney cancer. The Bove studies show actual real hazards relating to kidney cancer for individuals who were exposed to the toxic water at Camp Lejeune.

In my opinion, the analysis of the currently available evidence using the Bradford Hill framework makes it as likely as not that benzene is a cause of kidney cancer to a reasonable degree of medical certainty.

F. Perchloroethylene (PCE) and Kidney Cancer

1. Perchloroethylene (PCE)

Tetrachloroethylene (PCE) is a non-flammable colorless liquid. Tetrachloroethylene is a widely used chlorinated solvent. From the 1950s to 1980s, about 80% of PCE was used in dry-cleaning, and 15% in metal-cleaning and vapour degreasing. By the 1980's, the pattern of usage was changing, with about 50% of PCE used for dry-cleaning, 28% for chemical intermediates, and 10-15% for metal cleaning and degreasing. With the continuing decline of its use for dry-cleaning, PCE is now used primarily for producing fluorocarbons ATSDR, (2019).[68]

If PCE is discharged into the environment it can enter soil and groundwater. It can evaporate and can get below the soil surface to contaminate groundwater. PCE can also break down to trichloroethylene, dichloroethylene, vinyl chloride, and ethene through reductive dechlorination.[67]

2. IARC's Assessment of Perchloroethylene and Cancer Risk

The IARC 2014[16] Monograph 106 was published on the deliberations of a working group of experts that met from October 2-9, 2012, to address the case of PCE and cancer. IARC (2014) has classified tetrachloroethylene as "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals (Group 2A), and concluded that "positive associations have been observed for cancer of the bladder" in humans.

3. Systematic Reviews and Meta-Analyses

Mundt et. al. (2003)[69a] performed a systematic review of the epidemiological literature regarding the carcinogenic effects of PCE and kidney cancer. They included forty-four papers that were critically reviewed on 17 cancer sites being assessed for risk of association with PCE exposure. The authors did not find enough epidemiological evidence to support a conclusion that

occupational exposure to PCE is a risk factor for kidney cancer at that time. However, since that time there have been a multitude of studies that provide strong association between PCE and kidney cancer. Further, there was data in Mundt et. al. suggestive of a connection between PCE and kidney cancer. There was a multi-center case-control study by Mandel et. al. (1995)[69] of men and women exposed to dry-cleaning solvents, that found a statistically significant increased risk for renal-cell or kidney cancer. Elevated but not statistically significant risks were found by Ruder et al (2001).[70] Anttila et. al. (1995)[22] examined PCE-exposed employees from different occupations for kidney cancer and noted an increased risk for kidney cancer. The studies reviewed had some variability based on sample size, and accuracy of exposure assessment.

The evidence in the literature shows evidence of increased risk in some studies, equipoise and above risk in some studies and others with below equipoise risk regarding PCE exposure and kidney cancer. Based on the above, there is evidence that the risk of PCE exposure and kidney cancer is at least equipoise in the studies reviewed in Mundt et. al. (2003)[69a] and Mundt (2016).[70a]

4. Cohort Studies

Mandel et. al. (1995)[69] conducted an international multicenter case-control study including centers in Australia, Denmark, Germany, Sweden and the United States. The authors interviewed 1732 incident renal cell carcinoma cases and they selected 2309 controls. The authors classified study members according to exposure to dry-cleaning solvents and found a significant association between employment in the dry-cleaning industry with PCE exposure and renal cell carcinoma with a relative risk of 1.4 (95% CI: 1.1-1.7).

Anttila et. al. (1995)[22] conducted a retrospective cohort study of exposure to TCE, PCE, or 1,1,1-trichloroethane and increased cancer risk. A cohort of 2050 male and 1924 female workers was monitored for occupational exposure to these agents and was followed up for cancer incidence from 1967 to 1992. The cancer incidence was similar to the Finnish population. A cancer incidence risk ratio of 1.82 (95% CI: 0.22-6.56) was found. The study relied on biomarker monitoring for TCE and PCE exposure, so the risk of misclassification bias was low. The Anttila study revealed a modest increase in risk of kidney cancer for those exposed to TCE and PCE which was above equipoise at 1.1. The wide confidence interval was due to small numbers of cancer cases in the exposed cohort that results in a less precise risk estimate.

Blair A. et. al. (2003)[36] conducted a cohort study of workers in dry cleaning that was extended to further evaluate cancers risks associated with organic solvents. The cohort was 5,369 members of a dry cleaning union in St. Louis, MO from 1960 to December 31, 1993. The mortality of the cohort was compared to the US population and adjusted for age, year of death, race and gender. The SMR for kidney cancer was at 1.0 (95% CI: 0.4-2.0). The confidence interval was large and the risk estimate was less precise due to the small numbers of cases.

Boice et. al. (2006)[30] discussed above was a retrospective cohort mortality study of workers engaged in nuclear technology development and employed for at least 6 months at Rocketdyne (Atomics International) facilities in California, from 1948–1999. Expected mortality was calculated on race, age, calendar year and gender specific mortality rates.. Cancers of the kidney

were less than expected and the SMR was 0.69 (95% CI: 0.08-2.47). The low RR was most probably due to exposure misclassification and "healthy worker effect." The SMR for the worker group was below 1.0.

Calvert GM et al. (2011)[37] examined mortality relating to kidney cancer in a cohort study of dry cleaners. The study added 8 years of mortality follow-up for 1704 dry cleaning workers in four cities. The employees worked for greater than or equal to one year before 1960 in a shop where PCE was used as the primary solvent. An analyses of the life tables for mortality and ESRD morbidity was used. The study found an SMR of 1.14, (95% CI 0.37-2.67). When only exposure to PCE was used, a SMR of 1.35 (0.16-4.89) was found. The study serves as support that employment in the dry-cleaning industry and occupational exposure to PCE are associated with an increased risk for kidney cancer.

Lipworth et al. (2011)[26] conducted a follow-up of aircraft workers with exposures to different solvents. The workers were assessed for PCE exposure using a job-exposure matrix of historical chemical usage patterns. For 5,830 workers who had intermittent or routine PCE exposure, the SMR for kidney cancer was 0.8 (95% CI: 0.4-1.4). There were likely exposure mis-classification issues in a cohort with mixed solvent exposures which would bias the SOM towards the null.

Callahan et. al. (2019)[39] performed a follow-up cohort mortality study of 5,369 drycleaners from a union in St. Louis, MO. The study extended follow-up 22 years from 1993 through 2014 and included a link to the National Death Index. The analysis was done using Cox proportional hazards that used modeling of solvent exposure from union records. Mean PCE exposures found in the published monitoring studies ranged from 25 to 280 ppm. Current Occupational Safety and Health Administration's personal exposure limit for PCE is an 8-hour time-weighted average of 100 ppm. The models were adjusting for age, sex, and decade of union enrollment, and lag in exposure risk. The kidney cancer deaths were elevated and the SMR was 1.1 (95% CI:0.6-1.9). Increases in deaths were found for workers who joined the union in 1960 or later (SMR = 1.8 (95% CI: 0.7, 3.9) for kidney cancer. There was an exposure–response relationship for kidney cancer from medium exposure risk ratio of 4.1 (95% CI = 0.7, 22.5) to high exposure risk ratio of 24.4 (95% CI: 2.9, 201.6) (Ptrend = 0.004) in a 20-year lagged analysis. High exposure was also associated with lymphatic and hematopoietic malignancies (HR = 4.3; 95% CI = 1.4, 13.6).

Ruder et. al. (2001)[70] conducted a cohort study of 1,708 dry-cleaning workers identified from union records that were exposed to perchloroethylene (PCE) who had worked for at least a year before 1960. Vital status was updated through 1996 and life table analyses conducted. The results show that there was an increased risk of death from kidney cancer in the cohort as the SMR was elevated at 1.41 (95%CI:0.46-3.30). When the analysis was restricted to only those with PCE exposure history, the SMR increased to 1.73 (95% CI: 0.21-6.25). It was found that dry-cleaning workers have more cancer deaths related to the bladder and kidneys.

5. Case Control Studies

Aschengrau et. al. (1993),[72] conducted a follow-up case-control study of Cape Cod, MA drinking water contamination to assess kidney cancer risk in the people exposed to PCE contaminated drinking water. The authors noted 35 kidney cancer cases and while there were no cases in the

highest exposure category, there were PCE exposed cases in the low and medium exposure categories that produced an elevated risk ratio of 1.23 (95% CI:0.4-3.1).

Katz and Jowett (1981)[73] conducted a proportional mortality study of dry cleaning and laundry workers, using Wisconsin death certificates. The mortality patterns of 671 female laundry and dry cleaning workers for the period between 1963-1977 were analyzed, using Wisconsin death certificate data. Results failed to show an overall increase in malignant neoplasms in the study but elevated risks were observed for kidney cancer. The authors noted 7 observed deaths and 2.7 expected deaths that resulted in a PMR of 253 for kidney cancer.

Purdue MP, et. al. (2017)[38] conducted a case-control study of 1,217 cases and 1235 controls based on occupational history involving potential exposure to chlorinated solvents including PCE. The authors examined the association between kidney cancer and TCE, PCE and four other chlorinated solvents. High exposure to PCE was associated with kidney cancer.

Pesch B et al. (2000)[31] conducted a population-based case-control study that was conducted to examine urothelial cancer risk due to occupational exposure to TCE and PCE exposure. There were 1035 incident urothelial cancer cases and 4298 controls matched for region, sex, and age between 1991 and 1995. The German PCE cumulative exposure group for 30th, 60th, and 90th percentiles were examined. The results show a risk ratio at 30th percentile of 1.1 (95% CI:0.9-1.3); at the 60th percentile level the risk was 1.2 (95% CI 1.0-1.5) and at the 90th or substantial exposure level the risk was 1.4 (95% CI: 1.0-1.9) for men. The risk at the 30th percentile for women was 1.8 (95$^{\%}$ CI: 1-3), the risk at the 60th percentile was 1.0 (95% CI 0.6-1.9) and the 90th percentile was 0.7 (95%CI: 0.2-2.5). When the results were categorized using the JTEM the exposure-response trend was more apparent with risk ranging from 1.0 (95% CI: 0.7-1.5) at 30th percentile, 1.2 (95% CI: 0.8-1.7) at 60th percentile and 1.8 (95% CI: 1.1-3.3) at the 90th percentile level of exposure.

Christensen et al. (2013)[35] conducted a case-control study and utilized a team of chemists and industrial hygienists who translated job titles into potential exposures and case classification. The authors noted the risk ratio for any exposure was 1.6 (95% CI: 0.3-9.4) and the risk ratio for >90% cumulative exposure was 3.1 (95%CI: 0.4-24) so the authors did observe an increased risk for kidney cancer. There were some limitations in the study with very few exposed cases. This accounts for the wide confidence interval.

Karami S. et. al. (2012)[74] conducted a case control study of 1217 cases and 1235 controls that were frequency matched by age group, race, sex, and study center. The authors conducted personal interviews to assess exposure risk to PCE and risk of kidney cancer in drycleaning plants. The study results show that employment in the dry-cleaning industry, where exposure was primarily to PCE, was associated with elevated risk of renal cell carcinoma with an odds ratio of 2.0 (95% CI = 0.9-4.4). When the duration of exposure was considered, all exposed had a OR of 2.0 (95%CI:0.9-4.4) , <5 years had an OR of 1.8 (95%CI: 0.6-5.4) and > 5 years had a OR of 2.5 (95%CI: 0.4-14.4). This supports a monotonic trend for PCE exposure and kidney cancer and the test for trend showed a P value of 0.093. The authors stated that their findings provide support for an elevated risk of RCC in the dry-cleaning industries and suggest that these associations may be stronger for the RCC subtype.

Delahunt et al. (1995)[75] conducted a case-control study based on cancer-registry data and exposure assessment relied on occupational data recorded in the New Zealand Cancer Registry. The authors noted an increase in kidney cancer risk with an elevated of odds ratio of 1.92 (95% CI: 0.27-13.89). Thus, the study results do support an increased risk of kidney cancer in drycleaners in South Africa.

Ma J, et. al. (2009)[76] conducted an ecological study in New York City, USA of 900 dry-cleaning facilities using tetrachloroethylene for the years 1994-2004. The risk of cancer of the kidney was evaluated in association with living near a dry-cleaning facility using PCE. The unit of analysis was the population living in the same zip code area. The authors looked at discharge diagnoses for kidney cancer. The density of dry-cleaning facilities was a surrogate measure of exposure. Higher densities of dry-cleaning facilities using PCE were associated with higher rates of kidney cancer and the rate ratio was 1.15 (95% CI: 1.01-1.30).

These studies show a clear correlation between PCE and kidney cancer with multiple studies showing increased risk ratios and a causal relationship with kidney cancer.

6. Camp Lejeune Specific Studies

As noted above, ATSDR and Bove's studies showed elevated risk ratios for individuals exposed to the toxins at issue in the Camp Lejeune drinking water.

In Bove et. al. 2014a,[5] Camp Lejeune had elevated standardized mortality ratios for kidney cancer with moderately elevated SMR of 1.35 (95% CI: 0.84, 2.16). Within the Camp Lejeune cohort, non-monotonic exposure trends were noted for cumulative exposure to PCE and kidney cancer with a risk ratio for PCE for low cumulative exposure was 1.40 (0.54, 3.58). The risk ratio for medium cumulative exposure was 1.82 (0.75, 4.42) and the high cumulative exposure risk ratio was 1.59 (95% CI: 0.66-3.86) with a significant test for trend p value = 0.00009. The authors concluded that the risk kidney cancer deaths due to PCE exposure were significantly elevated and meets the above equipoise definition.

There were monotonic exposure responses for increased PCE exposure and kidney cancer in ATSDR 2018[7].

Further, the other studies cited above from Bove and the ATSDR show there were increases in kidney cancer incidences and mortalities for military personnel and civilians exposed to the water at Camp Lejeune. PCE was one of the toxins in the water at Camp Lejeune, which supports a causal association between PCE and kidney cancer.

7. Animal Experimental Data

PCE can adversely affects the kidney. Multiple studies have shown exposure to PCE causes nephrotoxicity in mice and rats, IARC (2014)[16] and end-stage renal disease among exposed dry cleaners.[67]

The animal experimental evidence of PCE causing kidney cancer is strong for PCE causing

kidney tumors in rats EPA (2012c). An exposure-response was observed for PCE causing Mononuclear Cell Kidney cancer (MCL) in male and female F344/N rats by inhalation at concentrations up to 400 ppm for 103 weeks (NTP, 1986a). The incidence of advanced stage MCL was significantly increased in both sexes at 400 ppm (NTP, 1986a). JISA, 1993[77] also observed a similar trend in incidence of MCL in male and female F344/DuCrj rats exposed by inhalation for 2 years that was seen in male rats at 600 ppm. The time to first occurrence of MCL was reduced in exposed female rats, relative to controls (JISA, 1993).[77] The NTP 2021 Report on Carcinogens noted that "PCE caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Inhalation exposure to PCE caused benign and malignant liver tumors in mice of both sexes and mononuclear-cell leukemia in rats of both sexes. In male rats, it also increased the incidence of benign and malignant tubular-cell kidney tumors, which are rare in rats (NTP 1986). Mice also developed liver tumors in both sexes administered PCE by stomach tube (NTP 1977, IARC 1979, 1987)".

8. Mechanistic Effects

The EPA did a toxicologic review of PCE in 2012. They used modeling tools for toxicokinetics, and examined the evidence from neurological studies, mechanistic, and studies of tumor latency, severity, and experimental animal cancer findings. PCE is metabolized in laboratory animals and in humans through at least two distinct pathways that includes oxidative metabolism via the cytochrome P450 pathway and through glutathione (GSH) conjugation followed by subsequent biotransformation to the cystine conjugate which can be cleaved by β-lyase or oxidized by flavin-containing monooxygenase 3 to form metabolites that include reactive thiokene.

Studies in both animals and humans indicate that metabolism of PCE slows down at higher exposure levels. Oxidative metabolism is the more dominant pathway in rodents.
A lower percent administered dose was metabolized at higher doses and less was metabolized in mice compared to rats. Pharmacokinetic modeling showed that at 50 ppm, only 1.5-1.7% of inhaled PCE would be metabolized. However, when the levels of PCE in the air was 0.001 ppm, the median estimate predicts that 36% of the inhaled dose would be metabolized (Bois et al., 1990)[78].

There is another mechanism of action for PCE metabolism relating to glutathione conjugation. The reactive metabolites of PCE bind to cellular macromolecules (Cichocki et al., 2017a).[17a] A more recent study by Luo et al. (2018)[80] found that, following treatment with both TCE and PCE, the flux in the glutathione conjugation pathway in mice was 21-fold higher for PCE than for TCE, indicating that more PCE is metabolized through the glutathione conjugation pathway compared to TCE. This is one way PCE and TCE metabolism differs.

Neurological Effects. Studies in rodents have shown that PCE alters the fatty acid pattern of brain phospholipids and amino acids, (Briving et al. (1986),[81] Kyrklund et al. (1990),[82] which helps to explain how PCE-induced neurotoxic effects occur. Other studies have shown that tetrachloroethylene can interfere with voltage-gated channels and neuronal receptors

Hepatic Effects. PCE effects in the liver result from metabolism to oxidative metabolites,

including trichloroacetic acid and dichloroacetic acid (Benane et al. 1996).[83] Rodents, especially mice, produce more trichloroacetic acid than humans (Hattis et al. 1993).[84] In addition, the trichloroacetic acid appears to be preferentially localized in the liver after oral exposure.

Renal Effects. PCE has been linked to an increase in kidney cancer in male rats following inhalation exposure to PCE (ATSDR 2019).[66] PCE has been linked to renal carcinogenicity including genotoxicity and cytotoxicity. This is thought to be related to α-2u-globulin accumulation in the proximal tubule epithelium. Peroxisome proliferation is also thought to be a contributing factor (Guyton et al. (2014);[85] IARC (2014),[16] NRC (2010).[86] The formation of genotoxic metabolites from S-(1,2,2-trichlorovinyl)-glutathione catalyzed by β-lyase, CYP3A, or flavin-containing oxygenases, and cell damage from lipid peroxidation due to glutathione depletion ATSDR (2019).[66]

Genotoxic Effects. PCE can cause genotoxic effects through the action of reactive metabolic intermediates generated during the metabolism of PCE (Cichoki et al. (2016);[17a] EPA 2012;[13] NRC 2010[86]). In vitro studies noted that metabolic activation (e.g., S9 fraction) is required or greatly enhances genotoxicity. Studies of the genotoxicity of PCE metabolites suggest that genotoxicity may occur through the formation of PCE-epoxide, trichloroacetyl chloride, and metabolites formed in the glutathione conjugation pathway.

9. NTP's 2021 Assessment of Tetrachloroethylene

The U.S. Department of Health and Human Services released the 15th Report on Carcinogens (ROC) January 2021.[44] The ROC is a congressionally mandated, science-based, public health document that the national Toxicology program (NTP) prepares for the HHS secretary. This cumulative report currently includes 256 listings of agents, substances, mixtures, and exposure circumstances that are known or reasonably anticipated to cause cancer in humans. In the 15th report, the NTP stated that PCE "…is reasonably anticipated to be a Human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and limited studies in humans." With regards to the dose-response relationship for PCE and cancer, the NTP noted that there were few human studies of kidney cancer that noted an exposure-response relationship between PCE and kidney cancer.

10. Bradford Hill Viewpoints

a. Strength of Association:

This viewpoint is mostly met in this case because a review of the epidemiological studies provides evidence supporting a moderate association between PCE exposure and kidney cancer. Mundt et. al. (2003)[69a] performed a systematic review of PCE and cancer. The authors did not find sufficient epidemiological evidence to support an association between occupational exposure to PCE and cancer at that time but there were some flaws in the analysis of that study. Further, more cohort and case-control studies have been conducted afterwards that do support an association between PCE and kidney cancer. The studies by ATSDR and Bove at Camp Lejeune,

and in Woburn, MA demonstrated an increased risk of kidney cancer and an exposure-response relationship between PCE and kidney cancer.

Bove 2014a[5] analyzed cumulative exposure to PCE and found Risk Ratios of 1.40 (low exposure), 1.82 (medium exposure) and 1.59 (high exposure). This supports causality.

Further, there were monotonic exposure responses for increased PCE exposure and kidney cancer in ATSDR 2018.

As noted above there is data from the actual people present at Camp Lejeune through the ATSDR and Bove studies that show associations between PCE and kidney cancer. These studies are not going to be reviewed in detail again, but they provide support for a causal association between PCE and kidney cancer.

Further, as cited above, there are a significant number of epidemiology studies that support an association between PCE and kidney cancer.

b. Consistency

The consistency viewpoint is supported by findings across several case control and cohort studies in Woburn, MA, Cape Cod, occupational studies and very significantly the actual data from Camp Lejeune. There are studies that do not show a causal relationship between PCE and kidney cancer, but these studies do not negate the clear relationship between PCE and kidney cancer found in studies cited above. There is consistency in findings across various study designs which supports the causal relationship between PCE and kidney cancer.

c. Specificity:

The viewpoint of specificity is hard to meet because there are many different diseases that can be caused by PCE. However, the epidemiological evidence discussed in this analysis is specific to the relationship of PCE and Kidney cancer and limited to those studies in which PCE exposure can be distinguished from other exposures. Thus, in my opinion, the evidence in support of this criterion is limited but supportive.

d. Temporality:

In the ATSDR, Bove, and other cohort and case-control studies, a significant association between TCE and PCE exposure and kidney cancer was found. In these studies, exposure preceded disease, providing evidence of temporality. Additionally, studies that have adjusted for a lag period in the onset of cancer have found a stronger association between PCE and Kidney cancer, which aligns with the latency period one would expect between exposure and the onset of a cancer such as Kidney cancer. Thus, in my opinion, the evidence in support of this criterion is strong.

e. Biological Gradient:

A review of the ATSDR and Bove Studies from 2017, 2018, 2014 and 2024 and the other cohort and case-control studies, indicates a real and known exposure-response relationship with respect to the levels or duration of PCE exposure and kidney cancer risk. This is shown above in the full analysis of the data on epidemiology and animal studies. Thus, in my opinion, the evidence suggests that evidence in support of this criterion is present but is more modest than TCE.

f. Biological Plausibility:

As discussed in other parts of this report, the mechanistic, experimental and animal evidence are supportive based on evidence of genotoxicity, immunosuppression, and carcinogenesis consistent with cancer changes related to miRNA, epigenetics, and chromosomal aberrations. Again, this is detailed in full above in this section of the report and is incorporated here by reference. Thus, in my opinion, the evidence in support of this criterion is strong.

g. Coherence:

The correspondence between the epidemiological evidence, animal experimental evidence and human and animal toxicological evidence noted by IARC, NTP and EPA HRA 2020 and confirmed by my review,] is consistent with coherence.

h. Experimental Evidence:

Experimental epidemiological evidence is not available for human exposures to PCE (and would be unethical to accomplish). However, it is important to note that the toxicological evidence regarding PCE's genotoxic and immunotoxic mechanisms are rooted in numerous sound experimental studies. These studies are all mentioned above and although it is unethical to prospectively test individuals and expose individuals to these known carcinogens, there is clear data as shown above of this type of evidence.

i. Analogy:

There is similarity between the likely mechanisms of action of PCE with other immunotoxic agents known to induce kidney cancer (e.g., TCE), which supports this viewpoint.

11. Conclusion: PCE Exposure More Likely Than Not Causes Kidney Cancer

In conclusion, the epidemiological evidence of the association between PCE and kidney cancer exists in many different epidemiological studies, exists in the animal data and there are reasonable and scientific mechanisms of action for this causal association.

In my opinion, the analysis of the currently assembled evidence using the Bradford Hill framework, makes it more likely than not that PCE is a cause of kidney cancer (and therefore also exceeds the "standard of at least as likely as not" standard prescribed by the Camp Lejeune

Justice Act.).

G. Vinyl Chloride and Kidney Cancer

1. Vinyl Chloride Generally

Vinyl chloride is often used to make polyvinyl chloride (PVC) plastic and vinyl products.[87,88] One of the largest uses of PVC is in the production of plastic piping and this contains some of the largest use of PVC resins.[87,88] Other important uses are in floor coverings, consumer goods, electrical applications and in the transport sector.[87,88] About 1% of PVC is used to produce vinyl chloride/vinyl acetate copolymer. [87,88] Minor uses of vinyl chloride (monomer) include the manufacture of chlorinated solvents (primarily 10 000 tonnes per year of 1,1,1-trichloroethane) and the production of ethylene diamine for the manufacture of resins.[87,88] Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, in the production of chloroacetaldehyde, as an aerosol propellant and in drug and cosmetic products; these uses were banned in the USA by the Environmental Protection Agency in 1974 (ATSDR, 2006).

2. IARC Assessment of Vinyl Chloride and Cancer

IARC's assessment of VC found that exposure to high levels of vinyl chloride in air has resulted in central nervous system effects (cns), such as dizziness, drowsiness, and headaches in humans. It found that chronic (long-term) exposure to vinyl chloride through inhalation and oral exposure in humans has resulted in liver damage. According to IARC, cancer is a major concern from exposure to vinyl chloride via inhalation, as vinyl chloride exposure has been shown to increase the risk of a rare form of liver cancer in humans.

Vinyl chloride was evaluated in previous IARC Monographs and was classified as a Group 1 Carcinogen based on increased risks for angiosarcoma of the liver and hepatocellular carcinoma (HCC). This was based on a case report of three cases of angiosarcoma of the liver in men who had been employed in the manufacture of PVC resins. This data supported a causal association between vinyl chloride and cancer (Creech & Johnson, (1974)[88].

3. Systematic Reviews and Meta-Analyses

There have been no meta-analysis or systematic reviews that assessed the risk of kidney cancer in vinyl chloride exposed worker cohorts or community population case control studies that I am aware of being published in the medical literature.

4. Camp Lejeune Specific Studies and Reports

As noted above, ATSDR and Bove's studies showed elevated risk ratios for individuals exposed to the toxins at issue in the Camp Lejeune drinking water.

Bove et. al. 2014a showed monotonic exposure trends for cumulative exposure to total volatile organic contaminants (TVOCs) (that included Vinyl chloride) and kidney cancer with a risk ratio for high cumulative exposure of 1.54 (95% CI: 0.63, 3.75) $\log_{10}$ β =0.06, 95% CI:-0.05, 0.17).

Specifically, Bove 2014a reviewed cumulative exposures to Vinyl Chloride and found increased HR of 1.66 (low exposure), 1.61 (medium exposure) and 1.51 (high exposure).

Further, the other studies cited above from Bove and the ATSDR show there were increases in kidney cancer incidences and mortalities for military personnel and civilians exposed to the water at Camp Lejeune. Of course, PCE was one of the toxins in the water at Camp Lejeune, which supports a causal association between PCE and kidney cancer.

5. Additional Studies

Mundt et. al. (2003)[69a] conducted a cohort study of 10,109 men who worked with VC between 1942 and 1972. The study follow-up continued through 12/31/1995 for twenty three years. Mortality from all causes of death showed a deficit of 17% (SMR 83, 95% CI 80 to 86), whereas mortality from all cancers combined showed a non-significant deficit of 4% (SMR 96, 95% CI 90 to 102). The results for kidney cancer were only mildly elevated at 1.08 with a 95% CI: 0.70 - 1.60).

Mundt et. al. (2016)[70a] did a follow-up of an earlier cohort study of men employed between 1942 and 1972 at 35 US vinyl chloride (VC) or polyvinyl chloride plants and followed the cohort for an additional 10 years through 31 December 2013. The Standardized Mortality Ratio and Cox proportional hazards analyses were used to evaluate mortality risks by cumulative VC exposure. The authors noted that mortality due to liver cancer and HCC were strongly associated with cumulative VC exposure over 865 parts per million-years (ppm-years). The authors also noted that deaths due to kidney cancer were elevated with an SMR=1.16, (95%CI 0.87 to 1.53).

Hu J. et. al (2002)[89] conducted a case control study that assessed the risk of kidney cancer from occupational exposure to vinyl chloride in Canada. Data was obtained from questionnaires on 1279 (691 male and 588 female) people with kidney cancer that had been recently diagnosed. The cancer was histologically confirmed as RCC and 5370 population controls came from eight Canadian provinces, between 1994 and 1997. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived using unconditional logistic regression. Compared with no exposure to the specific chemical, the adjusted ORs were 2.0 (95% CI: 1.2–3.3). The risk of renal cell carcinoma increased with duration of exposure to vinyl chloride. The duration of exposure ranged from 1-4 years, 5-19 years, and over 20 years and the corresponding risk ratios were 1-4 years - 0.8 (0.2–2.3); 5-19 years-1.7 (95% CI: 0.8–3.7) and over 20 years, the risk ratio was 4.7 (95% CI: 2.0–11.0).

6. Animal Experimental Data

The EPA found that there was sufficient evidence for the carcinogenicity due to vinyl chloride in experimental animals. Vinyl chloride has been documented to cause cancer in experimental studies of animals, with a wide range of concentrations. The studies consistently showed hepatic

cell carcinoma and angiosarcomas in mice and rats. Cancers have been linked to vinyl chloride exposure at other sites as well including the kidneys. Vinyl chloride caused cancer in mice, rats and hamsters, at several different tissue sites, and by different routes of exposure (IARC 1979). Vinyl chloride caused tumors of the blood vessels in the liver in mice and rats who inhaled vinyl chloride and in rats exposed orally. Inhaled vinyl chloride also caused mammary-gland tumors in rats, mice, and hamsters; skin tumors in rats and hamsters; Zymbal-gland tumors in rats; and lung tumors in mice. Since vinyl chloride was listed in the First Annual Report on Carcinogens, additional studies in rodents have been performed. Prenatal and perinatal exposure to vinyl chloride was also shown to increase the risk of hepatic hemangiosarcoma (IARC 2008).[88] Other studies reported that exposure to vinyl chloride caused tumors at additional tissue sites including the kidneys. Vinyl chloride was also noted to cross the placenta and cause cancer in the offspring of rats exposed by inhalation during pregnancy. Kidney cancers were slightly increased in exposed offspring of rats exposed to vinyl chloride.

7. Mechanistic Effects

Vinyl Chloride causes cancer and the mechanism of action occurs through genotoxicity that is mediated by reactive metabolites. Studies on the toxicokinetics, metabolism, genotoxicity, and molecular biology of vinyl chloride provide strong evidence that it can cause cancer. The mechanism underlying vinyl chloride-induced carcinogenicity includes many key steps in the metabolic pathway. The key events include metabolic activation of reactive metabolites, binding of the reactive metabolites to DNA, pro mutagenic action of these adducts leading to G→A and A→T mutations that affect the function of proto-oncogenes and tumour-suppressor genes at the gene and protein levels that leads to tumorigenesis (Bolt, 2005).

Vinyl chloride is oxidized to chloroethylene oxide and then forms chloracetaldehyde. The oxidation occurs in the cytochrome p450 metabolic pathway mediated by an enzyme that is triggered by ethanol. In rats, the metabolism of Vinyl chloride can become saturated at inhalation concentrations of 250 ppm. The rate of vinyl chloride metabolism in humans is approximately 50 µmol/h/kg.

The rate of Vinyl chloride elimination does not differ with repeated inhalations compared with single inhalation exposures. Vinyl chloride is metabolically activated in rats, and the two metabolites, chloroethylene oxide and chloracetaldehyde react with nucleic acid bases to form DNA and adducts. These adducts identified in vitro and in rats in vivo. Vinyl chloride causes increased production of etheno adducts in rats that have been found in different organs, such as the liver, lung and kidney, and lymphocytes.

Young animals are more susceptible to vinyl chloride exposure and formation of and persistence of vinyl chloride-induced adducts. In rats, adducts have been found equally in liver cells and in hepatocytes. Lipid peroxidation has been reported to cause the production of etheno adducts in humans.

It is unclear how the misincorporation of bases occurs following adduct formation.
Vinyl chloride is genotoxic in animals and humans. It is mutagenic, usually in the presence of

metabolic activation. Vinyl chloride causes DNA synthesis, increases the frequency of sister chromatid exchange in rat and human cells, and increases the frequency of chromosomal aberrations and micronucleus formation in mice, rats, and hamsters in vivo (IARC, 2008).

8. NTP 2021 Assessment of Vinyl Chloride Monomer

The IARC 2008 stated that epidemiological studies have continued to provide strong evidence for an association between vinyl chloride exposure and hepatic angiosarcoma (IARC 2008).[88] NTP reported that two studies also found the risk of liver cancer increased with higher exposure. It was reported that some studies also found an increase in cancer of the connective and soft tissues. NTP stated that the results of recent studies on lung cancer, lymphoma, and kidney cancer and vinyl chloride exposure were conflicting.

9. Literature Published after IARC

The EPA PCE Risk Assessment (2020)[87] determined that epidemiology studies confirmed that vinyl chloride is a known human carcinogen. IARC found: cancer potencies were derived for oral and inhalation exposure. An oral slope factor of 1.3 per (mg/kg-day) for continuous exposure during adulthood and 2.5 per (mg/kg-day) for continuous lifetime exposure from birth, based upon a chronic dietary study in female Wistar rats is recommended; an inhalation unit risk of 4.3 E-6 per (55g/m3) for continuous exposure during adulthood and 8.7 E-6 per (55g/m3) for continuous lifetime exposure from birth is also recommended, based upon exposure of male and female Sprague Dawley rats and Swiss mice, via inhalation, for a lifetime.

10. Bradford Hill Viewpoints

a. Strength of Association for Vinyl Chloride and Kidney Cancer:

This viewpoint is met in this case because despite conflicting results in the medical literature, both the Bove 2014a and Hu studies are extremely well conducted and found a causal relationship between vinyl chloride and kidney cancer. Based on the as likely as not standard (or equipoise), and consistent with ATSDRs' criteria for an equipoise and above determination, because there has been no metanalysis done for vinyl chloride and kidney cancer and there are two excellent quality studies that show moderate to high risk of kidney cancer from VC (including a monotonic dose response relationship for vinyl chloride exposure and kidney cancer) this viewpoint is met.

Further, Bove 2014a reviewed cumulative exposures to Vinyl Chloride and found increased HR of 1.66 (low exposure), 1.61 (medium exposure) and 1.51 (high exposure).

b. Consistency:

The consistency viewpoint is partially met by findings across the epiemiological studies that show a significantly positive increased risk of kidney cancer.

c. Specificity:

This viewpoint is difficult to meet because there are different diseases that are known to be caused by vinyl chloride. However, the epidemiological evidence discussed in this analysis is specific to the relationship of vinyl chloride and Kidney cancer. Thus, in my opinion, the evidence in support of this criterion is not strong because VC can cause hepatocellular carcinoma and angiosarcoma of the liver as well.

d. Temporality:

In the Bove studies and the Hu study, the authors found a significant association between vinyl chloride exposure and kidney cancer and exposure preceded disease, providing evidence of temporality. Thus, in my opinion, the evidence in support of this criterion is strong.

e. Biological Gradient:

The Hu (2002)[89] study found an exposure response relationship for vinyl chloride and kidney cancer. There are other studies, such as Bove 2014a and Mundt (2016)[70a], that have also found causal associations between vinyl chloride and kidney cancer. Thus, in my opinion, the evidence supports the association reaching at least equipoise if not higher for the risk of kidney cancer following vinyl chloride exposure.

f. Biological Plausibility:

The mechanistic, experimental and animal evidence are supportive based on evidence of genotoxicity. VC is a known genotoxic carcinogen. It is thought that this is attributed to the formation of DNA adducts by the highly reactive VC metabolite CEO. There is strong evidence linking etheno-DNA adducts with observed carcinogenicity. This increases confidence in extrapolating to low doses using either the ED10 method or the LMS model. Thus, in my opinion, the evidence in support of this criterion is strong.

g. Coherence:

The correspondence between the epidemiological evidence and the experimental toxicological evidence noted by IARC and NTP and EPA HRA 2020 [and confirmed by my review,] is consistent with coherence.

h. Experimental Evidence:

Experimental epidemiological evidence is not available for human exposures to PCE (and would be unethical to accomplish). However, it is important to note that the toxicological evidence regarding vinyl chloride's genotoxic and immunotoxic mechanisms are rooted in numerous sound experimental studies.

i. Analogy:

There is similarity between the likely mechanisms of action of vinyl chloride with other immunotoxic agents known to induce kidney cancer which supports this viewpoint.

11. Conclusion

In conclusion, the epidemiological evidence of the association between Vinyl chloride and kidney cancer exists, but is more limited than the other toxins at issue. There are multiple epidemiological studies indicating a connection between Vinyl chloride and Kidney cancer. (Hu 2002, Bove 2014a). In my opinion, the analysis of the currently available evidence using the Bradford Hill framework makes it at least as likely as not that Vinyl Chloride is a cause of kidney cancer to a reasonable degree of medical certainty.

H. Chemical Concentrations Associated with Kidney Cancer and Hazards to Humans

The following are examples found in the literature cited above of levels that are hazardous to humans and are known to be causally related to kidney cancer.:

1. **Bove FJ, Ruckart PZ, Maslia M, Larson TC. Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environ Health*. 2014;13:10**:
    a. Cumulative exposure of 1 – 3,100 μg/L-month of TCE
    b. Cumulative exposure to 1 - 155 μg/L-month of PCE;
    c. Cumulative exposure to 1 – 4,600 μg/L-month of exposure to all compounds at Camp Lejeune;
    d. 18 months of residence on base from 1975 to 1985.

2. **Bove FJ, Ruckart PZ, Maslia M, Larson TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environ Health*. 2014;13:68:**
    a. Employment on base for 2.5 years.

3. **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**:
    a. 110 – 11,030 ppb-months of TCE (cumulative);
    b. 36 - 711 ppb-months of PCE (cumulative);

c. greater than 711 ppb-months of TCE (cumulative).

4. **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:**

   a. 1-6 quarters stationed on base as a service member from 1975 to 1985;

   b. More than 21 quarters spent on base as a civillian worker from 1975 to 1985.

5. **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:**

   a. Cumulative exposure to 27-44 mg of PCE.

6. **Moore LE, Boffetta P, Karami S, et al. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. *Cancer Res*. 2010;70(16):6527-6536:**

   a. Exposure to a TCE concentration of $\geq$ 76 ppb.

7. **Andrew AS, Li M, Shi X, Rees JR, Craver KM, Petali JM. Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. *Int J Environ Res Public Health*. 2022;19(2):618:**

   a. Sustained exposure to 0-25 ppb of TCE.

8. **Parker GS, Rosen, S. Woburn: Cancer Incidence and Enviromental Hazards 1969-1978. Commonwealth of Massachusetts, Department of Public Health, 1981:**

   a. Exposure to a TCE concentration of 267 ppb.

These findings reinforce that even short exposures at relatively low levels can be hazardous to humans generally and are known to cause kidney cancer.

It is crucial to note that these levels are not the "floor" below which exposure is harmless. It is probable and likely that lower levels of exposure also carry increased risks. For example, if someone spends four hours in the sun without sunscreen and gets a sunburn, it's clear that four hours was enough to cause damage. However, that doesn't mean spending just two hours in the sun wouldn't also cause harm—it simply wasn't tested.

Randomized human controlled trials are both unethical and impractical in this context. Without randomized human controlled trials, researchers rely on real-world observational data to estimate exposure levels and assess whether they correlate with higher kidney cancer rates. Fortunately, the contamination at Camp Lejeune provides high-quality epidemiological data detailing how varying levels and durations of chemical exposure affected cancer risk.

I. Additive Effects of TCE, PCE, Vinyl Chloride, and Benzene on Kidney Cancer Risk

When considering the carcinogenic potential of simultaneous exposure to two or more known carcinogens, one may reasonably and scientifically anticipate that the carcinogens increase risk of cancer in an additive fashion—which is typically the default assumption when regulators assess chemicals that act through a common mode of action. There are other examples, as has been demonstrated by the example of asbestos and smoking in the causation of lung cancer where these chemicals interact in some way to increase the risk of kidney cancer beyond what would be expected by summing the individual risks (i.e., a supra-additive or multiplicative risk, also known as "synergy."

What can be appreciated is that, as discussed above, the mechanisms of action by which these chemicals are likely to cause cancer to have substantial overlap. The chemicals, including their metabolites have been shown to be genotoxic by causing damage to DNA and to cause chromosomal malformations. Both DNA damage and chromosomal aberrations are well known risk factors for cancers. TCE, PCE, VC and benzene are also known to suppress the immune system which includes surveillance for and destroying cancerous cells. Having a weakened immune system is well known to be a risk factor for cancer, including, specifically, kidney cancer. As such, in my opinion, it is reasonable to apply an additive approach to carcinogens with a common mode of action (as discussed above) and conclude that the combined risk of simultaneous exposure to TCE, PCE, vinyl chloride and benzene is more likely than not to be at least additive.

VI. Conclusion: TCE, PCE , Vinyl Chloride and Benzene Exposure at Least as Likely as not Causes Kidney Cancer

In conclusion, there is epidemiologic, toxicologic and mechanistic evidence in the literature that proves to a reasonable degree of medical and scientific certainty that TVOCs, TCE, PCE and Benzene cause kidney cancer more likely than not. Further, there is epidemiologic, mechanistic and other scientific and medical evidence that establishes that vinyl chloride meets the standard of equipoise or above as a cause of kidney cancer.

The levels of toxins in the water at Camp Lejeune were at levels that were hazardous to humans generally and known to cause kidney cancer. This is assessed given all of the literature cited above, including importantly, the literature analyzing the exact exposure of interest at Camp Lejeune. It also includes the body of other epidemiology literature the shows the levels of the different toxins known to be hazardous to humans and to cause kidney cancer.

Timothy M. Mallon.

Timothy M. Mallon, M.D., M.P.H., MS.

Attached as an exhibit is my CV that includes a list of publications from the past 10 years,

I have testified in one EEO case in the last four years for the Federal Occupational Health Program of HHS.

I charge $650 per hour for research, consulting, and testimony.

VII. LIST OF REFERENCES

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46. Under the NTP classification scheme the main categories are: 1. Known to be a Human Carcinogen: This classification is used when there is sufficient evidence from human studies that a substance causes cancer; 2. Reasonably Anticipated to be a Human Carcinogen: This category is used when there is limited evidence from human studies and/or sufficient evidence from animal studies. It suggests that a substance may cause cancer in humans, but the evidence is not as strong as for the first category; 3. Not Classifiable as to its Carcinogenicity to Humans: This is

used when the evidence is inadequate to make a determination about the substance's potential to cause cancer. Source: NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/go/roc15 (EndNote XML) DOI: https://doi.org/10.22427/NTP-OTHER-1003

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DR. MALLON'S RELIANCE FILES

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NORTH CAROLINA
SOUTHERN DIVISION

IN RE:	)	
	)	
CAMP LEJEUNE WATER LITIGATION	)	
	)	
This Document Relates to:	)	Case Nos.:
	)	
ALL CASES	)	7:23-CV-897
	)	
DAVID DOWNS	)	7:23-CV-01145-BO
	)	
DAVID WILLIAM FANCHER	)	7:23-CV-00275-BO-BM
	)	
ALLAN WAYNE HOWARD	)	7:23-CV-00490-BO
	)	
FRANK W. MOUSSER	)	7:23-CV-00667-BO-RN
	)	
JACQUELINE JORDAN TUKES	)	7:23-CV-01553-BO-BM

PLAINTIFFS' DESIGNATION AND DISCLOSURE OF PHASE II EXPERT WITNESSES WITH RESPECT TO KIDNEY CANCER

TIMOTHY M. MALLON'S RELIANCE FILES

Pursuant to Fed. R. Civ. P. 26(a)(2)(B)(ii) and the Stipulated Order Regarding Expert Discovery (Case Management Order No. 17) (D.E. 305), Plaintiffs hereby identify the facts, data, and publications considered by Timothy M. Mallon, MD, MPH, MS ("Dr. Mallon") in forming his opinions concerning general causation and kidney cancer.

Dr. Mallon's report, produced contemporaneously herewith, contains a thorough statement of the facts, data, and publications that he considered in forming his opinions, including a section entitled "List of References." Plaintiffs incorporate all facts, data, and publications referenced in Dr. Mallon's report as if fully listed herein. In addition, Plaintiffs identify the following facts, data, and publications considered by Dr. Mallon in forming his opinions:

1. Bove FJ, Ruckart PZ, Maslia M, Larson TC. Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Feb 19 (bates number CLJA_HEALTHEFFECTS-0000141103);

2. Bove FJ, Ruckart PZ, Maslia M, Larson TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Aug 13 (bates number CLJA_VA_RFP_4THSET_0000135084));

3. ATSDR Public Health Assessment, 2017 (bates number CLJA_HEALTHEFFECTS-0000000011);

4. ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases, 2017 (bates number CLJA_VA-RFP11-0000000131);

5. 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 (bates number CLJA_HEALTHEFFECTS-0000000214);

6. Bove FJ, Greek A, Gatiba R, Kohler B, Sherman R, Shin GT, Bernstein A. 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. 2024 Oct;

7. Bove FJ. Evaluation of cancer incidence among Marines and Navy personnel and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: a cohort study (Unpublished). 2024 Jan 29 (bates number CLJA_ATSDR_BOVE-0000060101);

8. Bove FJ, Greek A, Gatiba R, Boehm RC, Mohnsen MM. Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC base Camp Lejeune: a cohort study. Environ Health. 2024 Jul 3;

9. Andrew AS, Li M, Shi X, Rees JR, Craver KM, Petali JM. Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. Int J Environ Res Public Health. 2022 Jan 6;

10. Aschengrau A, Ozonoff D, Paulu C, Coogan P, Vezina R, Heeren T, Zhang Y. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health. 1993 Sep-Oct;

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23. Gérin M, Siemiatycki J, Désy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. Am J Ind Med. 1998 Aug;

24. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W, MURC Study Group. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. 2000;

25. Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med (Lond). 2002 May;

26. Jones P, Purdue, M. Invited Perspective: Insights into Exposure to Industrial Solvents and Cancer Risk at Camp Lejeune. 2024 Oct;

27. Purdue MP, Stewart PA, Friesen MC, Colt JS, Locke SJ, Hein MJ, Waters MA, Graubard BI, Davis F, Ruterbusch J, Schwartz K, Chow WH, Rothman N, Hofmann JN. Occupational exposure to chlorinated solvents and kidney cancer: a case-control study. Occup Environ Med. 2017 Mar;

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30. Varshavski, J, et al. Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. 2023;

31. EPA. Toxicological Review of Trichloroethylene. 2011 Sep;

32. ATSDR. Toxicological Profile for Trichlorethylene 2019 Jun;

33. National Toxicology Program. Report on Carcinogens, Fifteenth Edition: Tetrachloroethylene. 2021;

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35. EPA. Risk Evaluation for Perchloroethylene. 2020 Dec.;

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39. Water Modeling Data – Appendices I, J, H1 & K to Morris Malia's report in the above-captioned matter, dated October 25, 2024;

40. Deposition of Frank Bove;

41. Deposition of Morris Maslia;

42. The Camp Lejeune Justice Act;

43. *Westberry v. Gislaved Gummi AB*, 178 F.3d 257 (4th Cir. 1999);

44. *Nix v. Chemours Co. FC*, 2023 WL 6471690 (E.D.N.C. Oct. 4, 2023);

45. *Lightfoot v. Georgia-Pacific Wood Prods., LLC*, 2018 WL 4517616 (E.D.N.C. Sept. 20, 2018);

46. *Yates v. Ford Motor Co.*, 113 F. Supp. 3d 841 (E.D.N.C. 2015);

47. *Dew v. E.I. Du Pont de Nemours & Co.*, 2024 WL 4349883 (E.D.N.C. Sept. 30, 2024;

48. *In re Lipitor (Atrovastatin Calcium) Mktg., Sales Practices & Prods. Lia. Litig.*, 892 F.3d 624 (4th Cir. 2018);

49. Order, *In re: Camp Lejeune Water Litigation*, No. 7:23-CV-897, Dkt. No. 227 (E.D.N.C. June 5, 2024);

50. Order, *In re: Camp Lejeune Water Litigation*, No. 7:23-CV-897, Dkt. No. 247 (E.D.N.C. June 28, 2024);

51. All facts and data listed herein are either identified by bates number or are publicly available to and accessible by Defendant United States of America;

52. Dr. Mallon reserves the right to review and consider additional facts, data and publications;

53. Dr. Mallon reserves the right to consider the report of any other witness in this action; and

54. Dr. Mallon reserves the right to supplement this list of reliance files.

DR. MALLON'S CV

CURRICULUM VITAE

I. PERSONAL DATA

Name: Timothy M Mallon, MD, MPH, FACOEM
Address: 6508 Folded Leaf Square, Columbia, MD 21044 E-Mail/Tel#:mallonti03@gmail.com/ 443-370-9267

II. EDUCATION

Year	Degree	Type of Degree / Institution
1977	BPS	Bachelor Professional Studies Clarkson University Potsdam, NY
1986	MS	Resource Policy and Management School of Natural Resources University of Michigan
1987	MS	Environmental Health Hunter College City University of Ney York

III. POST GRADUATE EDUCATION

Year	Position	Type of Degree / Institution
1991	Medical Student	Doctor of Medicine Upstate Medical University Syracuse, NY
1992	Resident Year 1	Internship in Internal Medicine Tripler Army Medical Center, Honolulu, HI
1995	Resident Year 2	Master of Public Health School of Hygiene & Public Health Johns Hopkins, Baltimore, MD
1996	Resident Year 3	Occ. & Env. Medicine Residency US Army Public Health Center Edgewood Area-APG, Gunpowder, MD

IV. ACADEMIC APPOINTMENTS

Year	Position	Institution
2016	Professor/Adjunct Professor	Uniformed Services University
2012	Associate Professor	Uniformed Services University
2004	Assistant Professor	Uniformed Services University
1996	GPM Residency Faculty	Madigan Army Medical Center
1995	Teaching Fellow	Johns Hopkins University School of Medicine

V. CURRENT POSITIONS

Veterans Evaluation Services **Occupational Medicine** **Oct 2017 to Present**
Contract Consultant

Duties/Accomplishments Hours per work- 30
-Review Camp Lejeune & Agent Orange cases for service members and Veterans
-Review Gulf War Injury Claims, PACT Act TERA Claims and write medical opinion for VBA
-Address causal connection between exposure and related health outcomes

Montgomery County Retirement **Occupational Medicine** **Oct 2017 to Present**

Duties/Accomplishments Hours per work- 5
-Review disability cases for Montgomery County employees
-Apply standards of medical fitness for police, firefighters, other employees who are injured
-Advise management regarding whether medical documentation supports ongoing disability

Federal Occupational Health **Occupational Medicine** **Oct 2016 to Present**
Bethesda, MD **Contract Consultant**

Duties/Accomplishments Hours per work- 10
- Review ADA and FMLA cases for medical employability determinations
- Review preventive medicine informational booklets for technical accuracy
- Review respirator questionnaires and make recommendations for respirator wear

Department of Prev. Med. **Adjunct Professor** **July 2016 to Present**
and Biostatistics, USU

Duties/Accomplishments: Hours per week 10
- Serve as mentor to colleagues in PMB on current research projects
- Serve as Specialty Editor for the Textbook of Military Medicine

VI. PRIOR POSITIONS HELD

Health Research Sys Admin. **Occupational Medicine** **April 2022 to May 2023**
Comp. Injury Countermeasures **Consultant**

Duties/Accomplishments Hours per work- 10
-Review claims for injuries related to COVID-19 vaccinations
-Make determination of whether injury exists and causation
-Prepare recommendations for program director & legal review

Brown and Brown **Occupational Medicine** **April 2017 to Oct 2021**
Physician Disability Associates **Consultant**

Duties/Accomplishments Hours per work- 5
-Review disability cases for multiple insurance companies
-Apply standards of medical fitness for workability for injured/ill employees
-Advise management regarding whether medical documentation supports ongoing disability

Prior Jobs (Cont)	Duty Title	Dates
Department of Prev. Med. and Biostatistics, USU	**Professor and OEM Residency Director**	**July 2012 to June 2016**

Duties/Accomplishments: Hours per week 80

- Serve as Residency Director of the OEM Residency Program at USU,
- Selected, trained, and mentored OEM physicians for the Department of Defense.
- Revised training and assessment of residents to document ACGME competencies.
- Oversaw the training of 25 military OEM physicians from the US and Canada.
- Led efforts nationally among residency directors to implement ACGME Milestones, developed Milestones Translation Tools and shared best practices.
- Led ACOEM President's Task Force on Recruiting physicians to OEM
- Prepared the residency for an accreditation site visit, received maximal accreditation.
- Preceptor for Occupational medicine residents and medical students. Served as course director for four occupational medicine courses.
- Authored 8 book chapters and 45 peer reviewed journal articles
- Invited to speak at national meetings including the AOHC, APHA, and ACPM conferences and presented multiple poster and oral presentations.
- Chaired Residency Advisory Committees for OEM Residencies at Madigan and Pensacola and served on Committees for Dayton, Johns Hopkins, Walter Reed & USUSU Prev. Medicine

Dept of Preventive Med. and Biostatistics USU	**Vice Chair for Prev Med.**	**July 2010 to June 2012**

Duties/Accomplishments: Hours per week: 40

- Led efforts to support for Medical School Curriculum Reform, enlarged role of Public Health.
- Led the PMB leadership committee, providing policy guidance to the Chair
- Served on the Medical School Student Promotions Committee for the University.
- Served as Chair of the Preventive Medicine Leadership Committee.
- Participated on the Medical School Curriculum Committee representing the Department.

US Army Surgeon General's Office	**Consultant in OEM**	**July 2008 to June 2012**

Duties/Accomplishments: Hours per week 30

- Served as subject matter expert & consultant to Army Surgeon General.
- Provided OEH consults to 130 OH clinics worldwide.
- Recommended to Human Resources Command assignments/deployments of OEM physicians.
- Developed OH Improvements that focused on Staffing, Training, Credentialing & performance.
- Validated workload, staffing requirements successfully obtained $54.5 million for OH Program.
- Developed Army web-based OHP checklist to track OH clinic performance.
- Updated DoD OEM physician credentialing requirements for OH providers.
- Served as Chair of DoD OEM Working Group: Updated OH Surveillance Manual (DoD 6055.05M) that provides guidance on meeting federal law and regulations from OSHA.
- Led efforts to develop a DoD Biomarker Policy; developed DoD process/outcome performance measures for OH Program execution.
- Led VA and DoD efforts to revise the DoD Post Deployment Health Assessment DD FORM 2796 to better capture soldier deployment OEH health exposure concerns.

- Linked deployment exposures in Defense Medical Surveillance System with health outcomes.

Dept of Preventive Med. and Biostatistics | **OEM Residency Director** | **July 2004 to June 2010**

Duties/Accomplishments: Hours per week: 40
- Serve as Residency Director of the OEM Residency Program at USU,
- Selected, trained, and mentored OEM physicians for the Department of Defense.
- Revised training and assessment of residents to document ACGME competencies.
- Obtained additional training starts and successfully recruited best DoD physicians to the field.
- Doubled the size of the residency from eight to sixteen residents a year each year.
- Oversaw the training of sixty military OEM physicians from the US and Canada.
- Led residency programs nationally in implementing the Milestones and was commended by the National Capital Consortium and ACGME for these efforts
- Prepared the residency for two ACGME site visits and received the maximal accreditation.
- Preceptor for Occupational medicine residents and medical students. Served as course director for four Occupational medicine courses.
- Authored a book chapter and 13 peer reviewed journal articles and was invited to speak at national civilian medical meetings including the American OH Conference and Federal Occupational Health Conference and presented multiple poster and oral presentations.

Army Center for Public Health, Aberdeen Proving Grounds, Gunpowder, MD | **Director, OEM** | **August 2000 to July 2004**

Duties/Accomplishments:
- Served as Director of the OEM Directorate at the US Army Public Health Command.
- Provided oversight of Army OEH worldwide technical consultations.
- Supervised staff of 32 and managed a budget of over $3.9 million
- Developed policy and programs to reduce injuries, illnesses; lower FECA costs; obtained $1 million for pilot project demonstrated medical case managers effective and achieved a 4:1 ROI.
- Developed policy and advised commanders on FHP measures related to CRBN threats.
- Primary author of “Occupational Health” for the 2005 revision of DA Pamphlet 40-11.
- Assessed the quality of Army worker’s compensation, OH, and NBC surety programs.
- Developed OH templates for the electronic medical record, AHLTA.
- Standardized OH business practices world-wide as proponent for the MEDCOM commander.
- Coordinated OH support for Pentagon and World Trade Center response: developed exposure guidelines for contaminants to support consequence management and building re-entry
- Oversaw health assessments of 8000 soldiers who deployed to the WTC, Pentagon.

Madigan Army Med. Ctr, Fort Lewis WA | **Chief & Region Consultant Occ. & Env. Med. Service** | **July 1996 to August 2000**

Duties/Accomplishments: Hours per week: 50
- Served as Western Region Medical Cmd. OEM Consultant, oversaw delivery of care in eleven OH clinics in six states from Alaska to Southern California, supported 60,000 personnel.
- Significantly improved patient care, customer satisfaction, and OH clinic utilization.
- Standardized region respiratory protection, blood borne pathogens, latex allergy programs.
- Served as Chief of OEM at Madigan Army Medical Center, provided OM services for 10,000 employees and 40,000 active, guard and reserve solders.

- Supervised staff of 39 providers, His, OHNs and support staff.
- Updated Blood Borne Pathogen, Latex & Infection Control Programs, commended by Joint Commission for model infection control and disaster response programs.
- Chaired the Infection Control, member Hospital Executive, QA/QI and Safety Committees.
- Overhauled tuberculosis (TB) surveillance program to meet JC and OSHA requirements.
- Enhanced chemical response capability through training and exercises.
- Developed and implemented a region wide heat injury prevention plan.

Patterson Army Cmty Hospital, Fort Monmouth, NJ **Chief of Prev. Medicine** **July 1992 to June 1994**

Duties/Accomplishments: Hours per week: 45

- Oversaw delivery of PM services for five installations in NY and NJ;
- Supervised 4 MDs, 4 Industrial Hygienists, 7 nurses, 7 medics, 6 staff.
- Served on PACH Executive Committee, Chair of Infect Control Cmtte, hospital QA/QI.
- Upgraded OH services in region by organizing, updating SOPs and QI programs for PM that resulted in accessible, high quality care and commended by Joint Commission.
- Provided oversight of disease, injury prevention programs at two OH clinics, acute care clinic.
- Ensured workplace IH monitoring conducted that guided worker medical surveillance programs, obtained $250K for IH regional support.
- Provided Installation Commanders advice on community health, safety, lead poisoning and TB prevention and control plans, Travel Medicine, Post Deployment Surveillance for soldiers.

VII. CERTIFICATION AND LICENSURE

	Date
American Board of Preventive Medicine	
Board Certification in Occupational Medicine	16 Jan 1997

License: Maryland

VIII. MEMBERSHIP IN SCIENTIFIC SOCIETIES\PROFESSIONAL ORGANIZATIONS.

Association of Military Surgeons of the United States
American College of Occupational and Environmental Medicine (ACOEM) American College of Preventive Medicine (ACPM)

IX. FUNDED GRANTS

Title	Role	Funded (amount)	Grant Period
Exposure biomarkers & health outcomes in Iraq and Afghanistan, funded by DoD/NIEHS	PI	$4,650,000	9/8/2013 to 7/31/2019

X. PRIOR TEACHING ACTIVITIES

PMO 973	OEM Journal Club- Co-course Director
PMO 542	Clinical Occupational / Environmental Medicine- Co-course Director
PMO 655	Safety and Injury Prevention- Course Director
PMO 642	Clinical PM Services and Selected Topics in OEM- Co-course Director PMO
558	Intro to Preventive / Occ. Medicine Residencies- Co-course Director PMO
549	Toxicology- Course lecturer

XII. **OTHER PROFESSIONAL ACTIVITIES**

Specialty Editor, Textbook of Military Medicine in Occupational Medicine 2019
Special Editor J. Occupational and Environmental Medicine Supplement December 2019
- Deployment Environmental Exposures, Metabolomics, Inflammatory and microRNA
- Biomarkers and Health Outcomes Related to Burn Pits in Iraq and Afghanistan. 2016
- Federal Workers Compensation Programs, Published March 2015.
Editor, Mil. Med. Supplement July 2011, Hazardous Exposures in Military Populations. Reviewer, Military Medicine on Preventive and Occupational Medicine topics, 2007 to present.

XIII. **CLINICAL ACTIVITIES**

Staff occupational medicine physician, Federal Occupational Health, Bethesda, MD. Staff Occupational Medicine Physician Walter Reed Army Medical Center 2004 to 2016

XIV. **COMMITTEES** (national advisory, professional societies, hospitals)

Member, Residency Review Committee for Preventive Medicine, Accreditation Council for Graduate Medical Education- 7/2016 to 7/2019
Member, American Board of Preventive Medicine- 7/2016 to 7/2019

XV. **HONORS AND AWARDS**

ACOEM Award for Leadership in Academic Medicine and Research, April 2016 Delta Omega Public Health Honor Society as USU Faculty 2015
Defense Superior Service Medal 2016
US Army Surgeon General's "A-Designator" Award for Academic Excellence Recipient, Military Order of Medical Merit
Fellow, American College of Occupational and Environmental Medicine.

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Go, Young-Mi; Smith, Matthew R.; Walker, Douglas I.; Uppal, Karan; Rohrbeck, Patricia; Krahl, Pamela L.; Hopke, Philip K.; Utell, Mark J.; Mallon, Timothy M.; Jones, Dean P. "Metabolome- Wide Association Study of Deployment to Balad, Iraq or Bagram, Afghanistan". Journal of Occupational and Environmental Medicine. 61:S25-S34, December 2019.

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