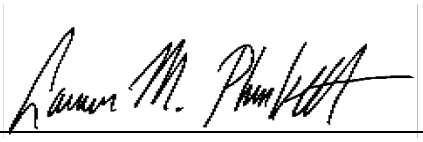
Exhibit 81

EXPERT REPORT OF
LAURA M. PLUNKETT, PH.D., DABT
December 9, 2024



Laura M. Plunkett, Ph.D., DABT

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and partner in a consulting company known as BioPolicy Solutions, LLC. BioPolicy Solutions has offices in Houston, TX and Ventura, CA, and is a consulting firm that works at the interface of biological science, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with development and marketing of existing products as well as new technologies. Before BioPolicy Solutions was formed in June of 2020, I was principal in the consulting firm known as Integrative Biostrategies (2001 to May 2020) and head of a consulting firm known as Plunkett & Associates (1997 to 2001). Attached to this report as Appendix A is a copy of my curriculum vitae.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral research was focused on the area of cardiovascular pharmacology, and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides. My training required my understanding of the mechanisms of action and basic pharmacology of drugs from all classes, as well as basic biological mechanisms that are associated both the desired effects of drugs (chemicals) and the adverse or toxic effects that can result from exposure to drugs (chemicals).

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neuroscience laboratory of the National Institute of Mental Health. My

research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug (chemical) actions that explain not only the desired effects but also the adverse or toxic effects that can result from exposure to drugs (chemicals).

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing toxicology and risks, as well as the regulation, of chemicals encountered by humans in their daily life. The chemicals I have examined include those regulated by the US Environmental Protection Agency (EPA), including the chemicals at issue in this case, *i.e.,* trichloroethylene, tetrachloroethylene, vinyl chloride, and benzene. A tool common to my work as a consultant would be risk assessment, including many projects where risks associated with exposure to chemicals in the environment (*e.g.,* air, water, soil) were at issue. The work included assessment of both short-term and long-term human health effects that might result from chemical exposure, as well as the association of chemicals with cancer.

7. With respect to experience that is directly relevant to the issues in this case, I have done a great deal of work on projects related to assessing the risks to human health following exposure to chemicals in the environment, including the four specific chemicals at issue in this case. I have worked on projects dealing with regulatory standards of chemical pollutants, including air and water pollutants, compliance with air and water pollution standards, as well as

methods for assessing the human health effects likely associated with chemical exposure. Among the clients that I have consulted with have been chemical companies and chemical trade organizations. A tool and generally accepted methodology common to all my work as a consultant would be risk assessment, including many projects where risks to human health related to exposure to chemicals in consumer products and/or the environment were at issue. As part of my work, I commonly review and rely on epidemiology data (studies in humans), as well as animal data and *in vitro* data to assess risks to human health that can result from certain types of chemical exposures.

8. As a pharmacologist and board-certified toxicologist, much of my consulting work has related to understanding and explaining the mechanisms of action of the toxic effects of chemicals of all types. I have expertise in pharmacokinetics, where I have designed clinical trials and analyzed pharmacokinetic data. I have taught pharmacology and toxicology to medical students and/or graduate students. I have lectured graduate students and law students on EPA regulations as they apply to all types of chemicals. Throughout my career, I have published dozens of peer-reviewed articles, which are listed in my curriculum vitae (Appendix A). I have served as a peer-reviewer for scientific journals in my capacity as a pharmacologist and toxicologist. In litigation, I have provided expert testimony and been qualified by both state and federal courts in the areas of pharmacology, pharmacokinetics, toxicology, risk assessment and EPA and FDA regulations. A list of my previous testimony for the past five years is included as Appendix B.

II. Scope of Work

9. I was asked to evaluate the human health effects associated with exposure to the four chemicals (perchloroethylene, trichloroethylene, benzene, and vinyl chloride) that were detected at varying levels over a number of years (1950's to 1980's) in the water that supplied Camp Lejeune, North Carolina, and to provide opinions as to whether the chemicals that contaminated the water posed a hazard to human health. My focus has been on the association of exposure to chemicals that contaminated Camp Lejeune water with bladder cancer in humans. I also was asked to provide opinions about the mechanisms that underly the toxic effects of these

chemicals in cells and tissues that might specifically relate to bladder cancer. I used standard methodology in performing my evaluation (described in Section III) and have relied on peer-reviewed scientific literature as well as government documents that represent consensus reviews and have undergone peer-review in forming my opinions in this case. All opinions expressed in this report are based on a reasonable degree of scientific certainty. I reserve the right to supplement my opinions if additional information becomes available that may be relevant to my opinions.

III. Information Reviewed

10. In the current case, I have been asked to provide opinions related to the human health hazards posed by exposure to chemicals that contaminated the water at Camp Lejeune, North Carolina. It is important to note that regulators and authoritative bodies around the world have continually performed comprehensive reviews of the human health hazards associated with exposure to the four chemicals that contaminated the water at Camp Lejeune, reviews that have occurred over a period of more than 40 years. The results of these comprehensive reviews have been consistent in terms of the hazards that have been linked to exposure to perchloroethylene, trichloroethylene, benzene, or vinyl chloride; the potential for each of these four chemicals to pose a cancer hazard to humans has repeatedly been affirmed. Also relevant to this case is the fact that over the course of my career, I have reviewed hundreds of scientific articles related to the human health effects that have been associated with exposure to the four chemicals detected in the water: perchloroethylene, trichloroethylene, benzene, and vinyl chloride. In this case, I have re-reviewed relevant scientific literature that I may have collected in the past, as well as regulatory documents and consensus reviews that relate to each of these chemicals that have been written by the EPA[1], other US regulatory agencies (*i.e.,* OSHA[2]; ATSDR[3] and CDC[4]), and the reports by expert panels convened by the International Agency for Research on Cancer (IARC) on all four of the chemicals numerous times over the last 40 years. My experience with each of these chemicals has included assessing human health hazards linked to each chemical,

[1] EPA refers to the U.S. Environmental Protection Agency.
[2] OSHA refers to the U.S. Occupational Safety and Health Administration.
[3] ATSDR refers to the Agency for Toxic Substances and Disease Registry.
[4] CDC refers to the Centers for Disease Control.

including the risks of cancer in humans. To provide a general summary, the relevant materials I have reviewed while working in this litigation include the following:

a) scientific literature relating to the biological effects and toxic effects of perchloroethylene, trichloroethylene, benzene, and vinyl chloride;

b) the federal regulations that exist setting forth methods to be used in assessing hazards to the four chemicals as well as standards that exist for the four chemicals that contaminated the water at Camp Lejeune; and

c) documents produced during the litigation that are, for example, reports of other experts in the litigation, the deposition of Frank J. Bove (dated 17 and 18 October 2024), or documents found on public sites (*e.g.,* the 2017 reports by the ATSDR related to Camp Lejeune[5]; cancer evaluations performed by IARC[6] on the four chemicals of interest in this case; cancer evaluations performed as part of the Report on Carcinogens (RoC) process[7] that is overseen by the National Toxicology Program (NTP) that have resulted in listings of the four chemicals of interest in this case.

It should be noted that most of the sources listed above are ones commonly used in my work as a pharmacologist, toxicologist, risk assessor, and regulatory consultant.

IV. Methodology Employed

[5] ATSDR (2017a) is entitled *Public Health Assessment for Camp Lejeune Drinking Water U.S. Marine Corps Base Camp Lejeune, North Carolina* (https://www.atsdr.cdc.gov/camp-lejeune/php/public-health-assessments/2017-public-health-assessment.html) and ATSDR (217b) is entitled *ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases* (https://www.atsdr.cdc.gov/sites/lejeune/docs/atsdr_summary_of_the_evidence_for_causality_tce_pce_508.pdf).

[6] IARC is an authoritative body where chemicals are nominated for review by expert panels put together to be specific to each chemical. IARC monographs that are produced from this process are not regulatory documents but are scientific reviews made by experts after a thorough review of the scientific literature and data. Monographs for chemicals may be periodically updated as new information becomes available.

[7] In 1978, the U.S. Congress amended Section 301(b)(4) of the Public Health Service Act, to require the Secretary of the Department of Health and Human Services (DHHS) to publish an annual report that contains a list of all substances that "are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed". The process of producing the list, known as the Report on Carcinogens, or RoC, results from periodic meetings and is a process managed by the NTP on behalf of DHHS. There have been 15 RoC processes to date, the 15th RoC being published in 2021.

11. In forming my opinions for this report, I used standard and generally accepted methods that apply in all my work as a pharmacologist and toxicologist that is related to assessing the safety and hazards of chemicals, both litigation and non-litigation projects. A tool I often use is a method known as human health risk assessment. Toxicologists routinely assess hazards to human health related to exposure to chemicals in the everyday environment using the basic principles of human health risk assessment, where hazard identification or assessment is the first step in the process. Toxicology is the scientific core of both hazard and risk assessment. Hazard and risk assessment methodology has been used for decades by a wide variety of governmental bodies to evaluate the safety of chemicals encountered in the everyday environment and to identify the potential hazards and specific adverse health effects that may occur in association with chemical exposures. Risk assessment is used in both non-governmental, non-regulatory, settings by scientists as well to understand the hazards and risks that can cause human harm. In 1983, the National Research Council (NRC) detailed the steps for risk assessment and described the methodology that is in use today as four basic steps: hazard identification, dose-response assessment (sometimes referred to as exposure-response assessment), exposure analysis, and characterization of risks (NRC 1983). As a result, hazard identification/assessment is a standard tool used by toxicologists when they are trying to determine if exposure to a chemical(s) poses a hazard to human health. It should be noted that hazard assessment is not a process that involves quantifying the level of risk to be expected in a population or in any individual that may be exposed to a chemical.

12. The methodology of human health risk assessment, including hazard identification and assessment, is a tool described in the *Reference Manual on Scientific Evidence, Third Edition* (NRC 2011) which is a resource developed for courts when evaluating methodology used by scientists in litigation projects. For purposes of clarity, hazard is defined as the potential of harm as a result of an exposure to a chemical while risk is the probability of harm occurring after exposure. I have been asked to address human health hazards associated with the four chemicals that contaminated the water at Camp Lejeune.

13. Like any project I work on that involves assessing the hazards that may be associated with exposure to chemicals, the first step was to identify, collect, review, assess, and

evaluate studies and analyses from the peer-reviewed scientific literature and government documents. This collection of documents was used as the basis of the information employed in my assessment. In this case, that literature review involved extensive searching of the published literature that described the effects of perchloroethylene, trichloroethylene, benzene, and vinyl chloride on human health, focusing on the potential for exposure to those chemicals to lead to bladder cancer in humans. I used available online databases (*i.e.,* PUBMED, TOXLINE, DIALOG) to systematically search the published literature for relevant literature. The papers I identified described the effects of the chemicals on living organisms, tissues and cells. Because these four chemicals have been commonly used or encountered by workers over the decades and have been linked to a variety of serious adverse effects on human health, they are regulated by federal and state governments in the US. As a result, some of the key resources I identified were toxicology textbooks and government documents that provided consensus opinions about some of the human health effects associated with exposure to trichloroethylene, perchloroethylene, vinyl chloride, or benzene. It should be noted, however, that even today, new associations between human disease and chemical exposures are emerging in association with these industrial chemicals (trichloroethylene, perchloroethylene, vinyl chloride, or benzene) based on the fact that new studies or research is performed. In my literature and document review, I employed another tool and generally accepted methodology known as a "weight-of-the-evidence" assessment.

14. A weight-of-the-evidence assessment involves evaluating individual studies or sources of information and determining what the studies or information describe, when considered as a whole. Therefore, weight-of-the-evidence methods were critical to defining the literature that identified the hazards to the chemicals that contaminated the water at Camp Lejeune, as well as defining the ways that exposure to those chemicals could lead to the human health hazard of cancer. I would note that in this case, although I have cited to, and rely upon, consensus reviews performed by authoritative bodies such as the EPA, ATSDR, IARC, and NTP, I also performed my own literature searches and retrieved and reviewed numerous individual papers or sources that may or may not have been referenced by others (*e.g.,* EPA, ATSDR, IARC) in a weight-of-the-evidence process in order to form my own opinions about

human health hazards posed by exposure to perchloroethylene, trichloroethylene, vinyl chloride, and benzene in water at Camp Lejeune.

15. With respect to my work related to understanding the mechanisms that underly the toxic effects on these chemicals in cells and tissues, this type of research is often used in causation analysis as laid out by Sir Bradford Hill in his seminal lecture about establishing causation between an exposure and a toxic effect or response (Hill 1965). In that lecture, Hill listed some basic conditions that should be met to link cause and effect (*e.g.,* strength of association, consistency, specificity, temporality, biologic plausibility, biologic gradient, coherence, experiment, analogy). The Hill criteria were never intended to be a "checklist" that must be followed blindly. Instead, they are a set of considerations that are used in cause-effect assessments (Rothman and Greenland, 1998. In: *Modern Epidemiology*. Rothman, K.J. and S. Greenland (eds.), Lippincott, Williams and Wilkins: Philadelphia, chapter 2). As Rothman points out, the only absolute criteria would be temporality, *i.e.,* the exposure or cause must precede in time the effect. I would also note that the Hill considerations are described in the *Reference Manual on Scientific Evidence* with respect to causation assessment.[8] As a toxicologist in this case, I have been asked to address some of the Hill considerations that might apply to the work I have undertaken.

16. As part of my work related to understanding the biological mechanisms that may underlie carcinogenesis related to exposure to the four chemicals that contaminated the Camp Lejeune water, I evaluated a large body of data and information and found that the following Hill considerations are particularly relevant to understanding those mechanisms:

- *Biologic plausibility* which addresses the question of whether there are biological mechanisms that elucidate why the effect observed (cancer in this case) may have occurred.
- *Experiment* which relates to the ability to collect data to analyze a cause-and-effect relationship, data that is commonly collected not in humans but in cells, tissues, or in animals.

[8] *The Reference Manual on Scientific Evidence, 3rd Edition*. National Research Council. 2011. Washington, DC: The National Academies Press. https://doi.org/10.17226/13163.

- *Analogy* which relates to consideration of experience with other similar chemicals that may share important biological properties.
- *Coherence* which addresses the question of whether the reported effect fits with the known pattern of disease.

17. As stated by Hill in discussing his consideration of biologic plausibility in particular, *"It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day."* (see page 10 of Hill 1965). This means that understanding the exact mechanism that underlies the effect being linked to any cause may not be understood. In this case, I have been asked to determine whether it makes sense that exposure to the contaminated water at Camp Lejeune would be a hazard to human health, and specifically, whether it makes sense that exposure to the contaminated water at Camp Lejeune might lead to bladder cancer in humans.

18. Because I am not a physician, I have not performed plaintiff-specific assessments of cause-and-effect for bladder cancer, a process that should rely on the results of a differential diagnosis in any individual. I must, however, consider the relevant pathways for exposure for plaintiffs in this case, as a general matter, to chemicals in the contaminated water at the base as part of my hazard assessment. Research performed by ATSDR (*e.g.,* Bove *et al.* 2014a; Bove *et al.* 2014b; Ruckart *et al.* 2015; Bove *et al.* 2024a; Bove *et al.* 2024b; ATSDR 2017a; ATSDR 2017b) confirms that all four chemicals contaminated the drinking water at Camp Lejeune and that the water was used for drinking, showering/bathing, and other daily activities. Therefore, in my evaluation of scientific information related to the hazard to human health associated with chemicals contaminating the water at Camp Lejeune, I considered data related to the potential routes of human exposure that have been linked to the contaminated water (water that was contaminated with perchloroethylene, trichloroethylene, benzene, and vinyl chloride). In addition to the route of exposure being important in my assessment, studies and information that address human exposure patterns in terms of duration and/or frequency of exposure also were relevant. This is because my focus was on cancer as a human health hazard and cancer does not occur immediately after exposure to a causative agent but instead develops some period of time

after the exposure occurred, a period of latency. The period of latency can last from several years to decades after exposure occurred (Nadler and Zurbenko 2013; Nadler and Zurbenko 2014; CDC 2015[9]) and requires an analysis for each disease.[10] Nadler and Zurbenko (2014) reported latencies for cancer development in humans based on modelling of cancer development that ranged from about two years to over 50 years.

19. I was trained in the use of human health hazard and risk assessment and weight-of-the-evidence methods as part of my undergraduate, graduate, and postdoctoral work in pharmacology and toxicology, as well as while working as a consultant to industry for the last 35 years. I would note that weight-of-the-evidence methodology is used as part of regulatory decision making by regulatory and scientific bodies such as EPA[11] and the U.S. Occupational Safety and Health Administration (OSHA),[12] and the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC).[13] The *Reference Manual on Scientific Evidence* also describes the use of weight-of-the-evidence by experts in the process of evaluating a body of data or studies.[14]

20. At the end of this report is attached a list of the published scientific articles cited throughout this report. Attached to this report as Appendix C is a complete list of all materials that I have reviewed and/or relied upon in forming my opinions in this case. All the opinions expressed in this report are based on a reasonable degree of scientific certainty. I reserve the right to supplement and refine my opinions as additional relevant information becomes available. I also reserve the right to review and comment on the reports and testimony of Defendants' experts.

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[9] https://www.cdc.gov/wtc/pdfs/policies/WTCHP-Minimum-Cancer-Latency-PP-01062015-508.pdf
[10] https://www.cdc.gov/wtc/pdfs/policies/wtchpminlatcancer2014-11-07-508.pdf
[11] *e.g.,* https://www.epa.gov/sites/production/files/2015-06/documents/acephate-103301_2015-06-29_txr0057153.pdf; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23160&CFID=65932199&CFTOKEN=24176705; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=65932266&CFTOKEN=97071893
[12] https://www.osha.gov/weightofevidence/woe_guidance.pdf
[13] http://www.who.int/phe/news/events/international_conference/Session2_DrStraif.pdf
[14] The *Reference Manual on Scientific Evidence*, 3rd Edition. National Research Council. 2011. Washington, DC: The National Academies Press. https://doi.org/10.17226/13163.

V. Human Health Hazards and Exposure to Contaminated Water at Camp Lejeune

21. In this case, the source of exposure to chemicals was contaminated groundwater that served as a source of drinking water for Marines and civilians that lived and worked at Camp Lejeune. In a 2017 report (ATSDR 2017a), the ATSDR provided data on levels of perchloroethylene, trichloroethylene, benzene, and vinyl chloride in drinking water from the two treated water sources (Tarawa Terrace and Hadnot Point) from 1975 to 1985. As described in the peer-reviewed literature by Bove and colleagues (2014a):

> *"Samples taken during 1980-1985 at United States Marine Corps (USMC) Base Camp Lejeune, North Carolina detected solvents in drinking water supplied by two of the base's eight treatment plants, Tarawa Terrace (TT) and Hadnot Point (HP). The TT supply wells were contaminated by an off-base dry cleaning business. The HP supply wells were contaminated by on-base sources: leaking underground storage tanks, industrial area spills and waste disposal sites. Contaminated supply wells in the TT and HP systems were shut down by February 1985." [see page 2 of the paper]*

In its 2017 Public Health Assessment (ATSDR 2017a), the agency stated the following regarding the exposure at Camp Lejeune:

> *"Thus, the historical record shows that in the past, people living and working at MCB Camp Lejeune were exposed to contaminated drinking water. As many as 1 million military and civilian staff and their families might have been exposed to the volatile organic compound (VOC)-contaminated drinking water during a 30plus year period."*

These sources of data make it clear that exposures were significant and would be considered "chronic" in terms of the number of years that Marines and civilians had been exposed to the contaminated water that contained trichloroethylene and perchloroethylene as well as two other volatile organic compounds (*i.e.,* vinyl chloride and benzene).

22. The four chemicals that contaminated the water at Camp Lejeune are ones that have been the subject of extensive study by toxicologists and regulators world-wide for decades due to their known toxic effects. As will be described here, it is not controversial that all four of the chemicals can be toxic to humans when they are exposed to them through breathing air,

drinking water, or when the chemicals contact skin. It also is not controversial that exposure to each of these chemicals individually poses a hazard to human health, a hazard that would include cancer in the case of all four chemicals. In this section, the human health hazards associated with these four chemicals will be discussed individually. In a later section of this report, the combination of chemicals will be discussed in the context of the hazard posed when humans are exposed to more than one chemical at the same time (mixtures of chemicals, Section VII of this report).

23. Hazard in the context of exposure to a chemical is whether there is a *potential for harm to be caused if exposure occurs*. Risk, a related term often encountered in the literature in the context of exposure to a chemical, is *quantifying what the probability of harm occurring is after an exposure occurs* and is typically performed based on selection of one dataset, usually in animals, that provides enough information to quantify the relationship between an exposure and a toxic effect and also allows for prediction of a level of risk that would then apply to a population of similarly exposed humans. Risk assessment is a predictive tool. As discussed in the peer-reviewed literature (Wilson and Crouch 1987):

> *"Risk assessment is presented as a way of examining risks so that they may be better avoided, reduced, or otherwise managed. Risk implies uncertainty, so that risk assessment is largely concerned with uncertainty and hence with a concept of probability that is hard to grasp."*

24. The question being asked in terms of effects on humans that can be produced by a chemical hazard is: Does the agent cause adverse human health effects?[15] As part of answering that question, toxicologists will consider data collected in cells and tissues (*in vitro* data), in animals (*in vivo* data), and in humans (if available). During the hazard assessment process, the studies that the toxicologist typically will rely upon would be ones where routes of exposure are relevant to the issue being addressed. Thus, it was important in this case to define the relevant routes of exposure to consider when I evaluated the scientific literature and regulatory documents. As already mentioned, the water at Camp Lejeune was contaminated with chemicals

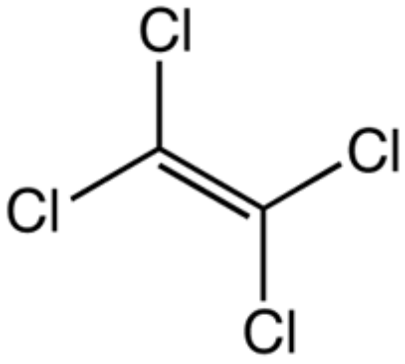
[15] Faustman, E.M. 2019. General principles of toxicology. In: *Casarett & Doull's Toxicology:The Basic Science of Poisons, 9th Edition*. C.D. Klaassen (ed.), McGraw-Hill: New Uork, NY, chapter 4, page 128.

and that water was used for drinking as well as showering and other daily activities. Thus, the water could have been ingested (oral exposure) and it could contact the skin as well (dermal exposure). Additionally, perchloroethylene, trichloroethylene, vinyl chloride and benzene are all "volatile organic" chemicals. The term "organic" means the chemicals are composed mainly of carbon and hydrogen atoms but also include atoms of other elements such as nitrogen, oxygen, halogens (chlorine, fluorine), phosphorus, and sulfur. "Volatile" means that the chemicals can readily evaporate into air from a liquid state under certain environmental conditions (such as heating of water). The volatile nature of these chemicals means that ingestion and dermal contact are not the only relevant routes of human exposure to consider. These chemicals can volatilize into air and thus humans could be exposed by breathing them in air. As a result, studies and toxicology information that related to oral, dermal and inhalation exposure all were relevant to my hazard assessment. Finally, as part of hazard assessment, the toxicologist must apply their education, training and experience when reviewing data and information and when they draw their final conclusions about whether the data and information are sufficient to have identified a hazard to human health, *i.e.,* the potential to cause harm.

A. Perchloroethylene

25. Perchloroethylene (C_2Cl_4; Cas Number 127-18-4) is also known by the chemical names of tetrachloroethylene and tetrachloroethene. Its structure is shown below in Figure 1.[16]

Figure 1: Structure of Perchloroethylene



[16] https://pubchem.ncbi.nlm.nih.gov/compound/Tetrachloroethylene#section=2D-Structure

The human health hazards associated with exposure to perchloroethylene are well-known and have been the subject of numerous scientific review papers (*e.g.*, Cichocki *et al*. 2016; Ceballos *et al.* 2021) as well as US government documents (*e.g.,* EPA 2012; EPA 2020a; EPA 2022 ATSDR 2019a; NTP 2021a), and documents related to human health hazards associated with perchloroethylene authored by other authoritative bodies (*e.g.,* IARC 1979; IARC 1987; IARC 1995; IARC 2012; NRC 2010; ECHA 2008[17]). Each of the government bodies and authoritative bodies who have produced consensus reviews related to perchloroethylene and human health hazards based their decisions on the same type of scientific evidence (peer-reviewed published studies) that I have relied upon in forming my opinions in this case and includes much of the same evidence I cite in this report. Of course, my research has the benefit of the availability of more recent supportive evidence. A review of all these documents shows that the principal adverse human health effects linked to exposure to perchloroethylene, regardless of the route of exposure, have included neurological effects, liver effects, kidney effects, reproductive effects, developmental effects, and cancer. The EPA even proposed to ban perchloroethylene for all consumer uses and many commercial uses because it is a chemical known to cause serious health risks such as neurotoxicity and cancer.[18] Perchloroethylene has been classified as a *"probable human carcinogen"* by IARC (2012), as *"likely to be carcinogenic in humans by all routes of exposure"* by EPA (2012), and as *"reasonably anticipated to be a human carcinogen"* by NTP (2021a).

26. Like most toxicologists would do, IARC as well as NTP based its conclusions in part on evidence of cancer in experimental animals. As discussed in textbooks regarding human health hazard and risk assessment (*e.g.,* Faustman 2019), animal studies have been a key component of the hazard and risk assessment process for toxicologists for over forty years (Boorman *et al.* 1994). Such studies allow for the ethical examination of a range of doses (from very low to very high) in the same study and allow for examination of changes at the tissue level (after sacrifice of the animals). In this case, also available for my review were results from three lifetime rat studies and three lifetime mouse studies that had been conducted with

[17] https://echa.europa.eu/substance-information/-/substanceinfo/100.004.388
[18] https://www.epa.gov/newsreleases/epa-proposes-ban-all-consumer-and-many-commercial-uses-perchloroethylene-protect

perchloroethylene, one where rats and mice were exposed by oral dosing (NCI 1977) and two where rats and mice were exposed by inhalation (NTP 1986a; JISA 1993). Perchloroethylene was carcinogenic in both rats and mice, including animals of both sexes, with tumors or cancer evident across the studies in multiple tissues (*e.g.,* liver, kidney, mononuclear cell leukemia, testes, brain, spleen). I evaluated these studies as well as the reviews that were provided by both IARC (IARC 2012) and EPA (EPA 2012) and found that these studies support my overall conclusion that perchloroethylene exposure poses a cancer hazard.

27. I also reviewed the body of data and information related to perchloroethylene exposure and bladder cancer in humans since that relationship was a focus of my hazard assessment. In addition to literature searches that I performed, the evaluation of perchloroethylene and cancer by IARC (IARC 2012) as well as more recently by EPA (EPA 2020a) provide bibliographies and description of numerous human epidemiological studies that have reported on the specific endpoint of bladder cancer after exposure to perchloroethylene. The following are epidemiological studies that report data and analyses related to the risk of bladder cancer in humans exposed to perchloroethylene: (1) eight cohort epidemiological studies (Boice *et al.* 1999; Travier et al. 2002; Blair *et al.* 2003; Lynge *et al.* 2006; Wilson *et al.* 2008; Calvert *et al.* 2011; Selden and Ahlborg 2011; Silver *et al.* 2014); and (2) ten case-control studies (Schoenberg *et al.* 1984; Steineck *et al.* 1990; Burns and Swanson 1991; Ashengrau *et al.* 1993; Swanson and Burns 1995; Pesch *et al.* 2000; Gaertner *et al.* 2004; Colt *et al.* 2011; Christensen *et al.* 2013; Hadkhale *et al.* 2017). In addition to my review of these studies, many were given a detailed evaluation by IARC (2012a) and EPA (EPA 2012; EPA 2020a). After weighing the strengths and weaknesses of the epidemiological studies, IARC's expert panel concluded that there were "positive associations" for cancer of the bladder associated with perchloroethylene exposures. Again, IARC's basis and rationale was based upon the same evidence supporting my opinions. In fact, however, my opinions are further supported by the growing basis in the scientific literature that continued to develop after IARC reached its conclusions. ATSDR (2017b) also addressed the issue of bladder cancer and perchloroethylene exposure due to exposure to contaminated water at Camp Lejeune specifically and concluded that there was sufficient evidence of causation for perchloroethylene and bladder cancer in the people that lived and worked at Camp Lejeune. Although I assume that others will be addressing these studies as

part of a full causation analysis, I reviewed each of these studies as part of my overall weight-of-the-evidence for bladder cancer as a human health hazard linked to exposure to perchloroethylene. After my review of all of these studies, I found that they support my overall conclusion that cancer, including specifically bladder cancer, is a human health hazard that has been associated with exposure to perchloroethylene in humans.

28. It is important to note that in the case of all four of the chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, benzene, and vinyl chloride), metabolism leads to production of active or toxic metabolites that are believed to be responsible for the adverse effects associated with these chemicals in biological systems. In the case of perchloroethylene specifically, the toxic metabolites are formed after oxidation of the chemical by liver enzymes (known as cytochrome P450 or "CYP" enzymes) or after conjugation by glutathione (*e.g.,* Lash *et al.* 2007; Luo *et al.* 2018); the enzyme CYP2E1 has a specific role in the production of reactive perchloroethylene metabolites (*e.g.,* Luo *et al.* 2018), and the same enzymes are found in other tissues in the human body including the kidneys (*e.g.,* Liu and Baliga 2003; Moore *et al.* 2010; Abdelmegeed *et al.* 2017). More detail on the role of that metabolism of perchloroethylene, and each of the other three chemicals that contaminated the water at Camp Lejeune, may play as part of the mechanism underlying bladder cancer is discussed in Section VI.

29. A characteristic of perchloroethylene relevant to this case, and to the cancer hazard posed by the chemical, is its pharmacokinetics/ toxicokinetics; pharmacokinetics/ toxicokinetics is the study of the way a chemical is absorbed, distributed, metabolized, and eliminated from the body. The toxicokinetic profile of perchloroethylene has been extensively reviewed (*e.g.,* Cichocki *et al.* 2016; EPA 2012; EPA 2020a; ATSDR 2019a; IARC 2012a). As noted by the ATSDR in its public health risk assessment (ATSDR 2017a), there are inter-relationships relevant to three of the four chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, and vinyl chloride) such that perchloroethylene can be degraded in the environment to form trichloroethylene as well as vinyl chloride. This means that trichloroethylene and vinyl chloride that contaminated the water at Camp Lejeune may be present as a result of environmental degradation of perchloroethylene (Vogel and McCarty 1985;

https://www.waterboards.ca.gov/gama/docs/coc_pce.pdf), as well as being present as a result of direct contamination of the water from other sources.

30. Perchloroethylene is almost completely absorbed after inhalation and oral exposures (essentially 100% of the chemical that is inhaled or ingested will be absorbed into blood; as reviewed in EPA 2020a; Monster *et al.* 1979a; Pegg *et al.* 1979; Schumann *et al.* 1980; Frantz and Watanabe 1983; Opdam and Smolders 1986; Dallas *et al.* 1994a; Dallas *et al.* 1994b; Dallas *et al.* 1995). After dermal or skin contact, absorption of perchloroethylene in a liquid form has been shown to be extensive as well (EPA has assumed 100% absorption can occur after dermal contact or immersion of skin in perchloroethylene in solution; EPA 2020a). After oral absorption, perchloroethylene is metabolized in the liver on a first pass[19] of blood through the body, while after inhalation exposures to perchloroethylene, a significant portion of the compound can be eliminated in the breath before undergoing liver metabolism (*e.g.,* reviewed in EPA 2012; Monster *et al.* 1979a; Monster *et al.* 1983; Monster 1986). Any perchloroethylene that is not exhaled immediately would undergo metabolism in the liver only after blood circulation through the liver. Perchloroethylene and its metabolites are distributed to all tissues in the body and can cross the blood-brain barrier as well as the placenta (Dzubow *et al.* 2010). The chemical accumulates in fatty tissues and in breast milk due to the lipophilicity[20] of the compound (Cichocki *et al.* 2016).

31. As a result of its accumulation in fat in the human body, the compound and its metabolites stay in the body for an extended period after an exposure has occurred. As EPA stated (EPA 2012): *"Long residence time in adipose tissue can result in increasing body burden with continuous or repeated exposures."* [see page 45 of 1077 of EPA 2012] This statement was made based on information found at least in part in studies in workers or human volunteers that had been exposed to perchloroethylene (*e.g.,* Fernandez *et al.* 1976; Monster 1979; Skender *et al.* 1991). The issue of accumulation in fat tissue is important in cases like the current case where daily exposures in water could occur and, as result of accumulation in fat, can lead to higher

[19] The term "first pass metabolism" is often used by pharmacologists and toxicologists to describe this process; such an effect is bypassed when chemicals are inhaled through the lungs or when exposure is due to sublingual, nasal, rectal, or skin application of a chemical.
[20] Lipophilicity means the chemical readily dissolves in fat or other lipid-rich tissues.

levels of perchloroethylene in the body over time (internal dose) than might be reflected by the level detected in water (external dose). This prolonged residence time in the body of perchloroethylene and its metabolites is reported as a "half-life" in the body; the term "half-life" is a measure of the amount of time it takes for 50% of the level of the chemical in blood to be eliminated from the body. The half-life of perchloroethylene's toxic metabolites in the human body has been reported to be 144 hours (as presented by EPA 2020a; Ikeda 1977) which means that significant levels of the metabolites can still be found in cells and tissues before a new exposure may have occurred when exposures to perchloroethylene are a daily occurrence. Moreover, general principles of pharmacokinetics dictate that accumulation of the parent compound, perchloroethylene, in adipose tissue (fat) can lead to continued metabolic conversion of the parent compound as it is released from adipose tissue*, i.e.,* ongoing exposure over time even days[21] after exposure has occurred. In the case of people exposed to the contaminated water at Camp Lejeune where many lived and worked on the base, exposure periods would be expected to episodic but occur more than once a day, meaning that accumulation of any perchloroethylene that would be absorbed into the body due to contact with the contaminated water would lead to the presence of some level of the chemical in the body at levels higher than might be predicted by only considering a measured level in the water and a single exposure.

32. As already mentioned, the metabolism of perchloroethylene in the body leads to the production of toxic metabolites that are responsible for the adverse effects the chemical has on biological systems, including the mechanisms that lead to cancer. Importantly, the metabolism of perchloroethylene to toxic metabolites is saturable at higher levels of exposure (as reviewed in EPA 2020a and ATSDR 2019a; Ohtsuki *et al.* 1983; Seiji *et al.* 1989; Volkel *et al.* 1998; Philip *et al.* 2007; Cichocki *et al.* 2016), meaning that *more extensive metabolite formation occurs at low levels of exposure* as compared to higher exposure levels. This is important in the current case because the exposures experienced at Camp Lejeune would have been to lower daily levels as compared to exposures reported in epidemiological studies performed in worker populations in the past.

[21] The issue is "days" relates to the half-life of 144 hours that has been reported for perchloroethylene, which would equate to a period of about six days.

33. Once perchloroethylene's metabolites have been formed, either by enzymes present in the liver or the kidneys, they are excreted through the kidneys into urine. The time that urine remains in the body in humans can vary due to lifestyle factors or diseases; on average, adults generally void five to six times a day but no more than once after retiring to bed (Wrenn 1990[22]). This would mean that perchloroethylene metabolites could remain in contact with bladder tissue for at least four to five hours at a time. Specific reactive/toxic perchloroethylene metabolites will be discussed in Section VI of this report in connection with my discussion of the Hill considerations that are supportive of a cause-and-effect relationship between exposure to contaminated water at Camp Lejeune and bladder cancer in people that lived or worked on the base.

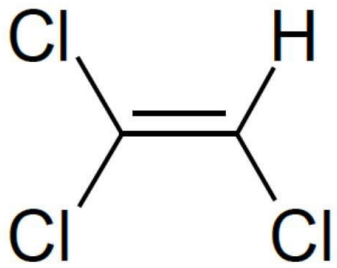
34. Based upon my education, training and experience, and considering the data and information identified and reviewed, it is my opinion to a reasonable degree of scientific certainty that it is at least as likely as not that exposure to perchloroethylene from contaminated water at Camp Lejeune was hazardous to human health generally, that exposure to the Camp Lejeune water contaminated with perchloroethylene specially is hazardous to human health, and, further, that the human health hazard would include the development of bladder cancer. This conclusion was reached based on: (1) review of data collected in numerous toxicological studies (studies in cells and tissues, animals and in humans); (2) data showing that perchloroethylene was one of the four chemicals that contaminated the water at Camp Lejeune for decades; (3) consideration of the fact that the routes of exposure for humans that may have lived and worked at Camp Lejeune and were exposed to the contaminated water would have encompassed multiple relevant routes of exposure addressed in toxicological studies and human epidemiological studies (*i.e.,* ingestion of water, inhalation of volatilized perchloroethylene, and dermal contact with water); (4) consideration of the toxicokinetic profile of perchloroethylene that would impact human health hazard such as formation of reactive metabolites that have been linked to mechanisms of cancer (this information is discussed in Section VI of this report) and accumulation of the chemical in body tissues with repeated exposures; and (5) my training and experience in human health hazard assessment, including experience with perchloroethylene human health hazard and risk assessment.

[22] https://www.ncbi.nlm.nih.gov/books/NBK291/

B. Trichloroethylene

35. Trichloroethylene (C_2HCl_3; CAS Number 79-01-6) is also known by the chemical name of trichloroethene. Its structure is shown below in Figure 2.[23]

Figure 2: Structure of Trichloroethylene



Like perchloroethylene, the human health hazards associated with exposure to trichloroethylene are well-known and have been the subject of numerous scientific review papers (*e.g.*, Chiu *et al.* 2013; Rusyn *et al.* 2014; Cichocki *et al.* 2016; Lash 2024) as well as US government documents (*e.g.,* EPA 2011; EPA 2020b; ATSDR 2019b; NTP 2015; NTP 2021b), and documents related to human health hazards associated with trichloroethylene authored by other authoritative bodies (*e.g.,* IARC 1979; IARC 1987; IARC 1995; IARC 2012; NRC 2006; Health Canada 2005; ECHA[24]). Each of the government bodies and authoritative bodies who have produced consensus reviews related to perchloroethylene and human health hazards based their decisions on the same type of scientific evidence (peer-reviewed published studies) that I have relied upon in forming my opinions in this case and includes much of the same evidence I cite in this report. Of course, my research has the benefit of the availability of more recent supportive evidence. Available consensus review documents have concluded that the principal adverse human health effects linked to exposure to trichloroethylene, regardless of the route of exposure, have included immunological and lymphoreticular effects, neurological effects, reproductive effects, developmental effects, and cancer. In the most recent systematic review (EPA 2020b), the EPA listed the human health hazards that the agency had identified in association with

[23] https://pubchem.ncbi.nlm.nih.gov/compound/Trichloroethylene#section=2D-Structure
[24] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/124309

trichloroethylene exposure and those hazards included liver toxicity, kidney toxicity, neurotoxicity, immunotoxicity, reproductive toxicity, developmental toxicity, and cancer. Trichloroethylene has been classified as *"carcinogenic to humans"* by IARC (2012), as *"carcinogenic in humans by all routes of exposure"* by EPA (2011), and as *"a known human carcinogen"* by NTP (2015).

36. Like most toxicologists would do, IARC as well as NTP based its conclusions in part on evidence of cancer in experimental animals. As discussed in textbooks regarding human health hazard and risk assessment (*e.g.,* Faustman 2019), animal studies have been a key component of the hazard and risk assessment process for toxicologists for over forty years (Boorman *et al.* 1994). Such studies allow for the ethical examination of a range of doses (from very low to very high) in the same study and also allow for examination of changes at the tissue level (after sacrifice of the animals). In this case, also available for review were the results from chronic exposure trichloroethylene exposure studies in rats and in mice, where rats and mice were exposed by oral dosing (NCI 1976; Van Duuren *et al.* 1979; Maltoni *et al.* 1986; Herren-Freund 1987; NTP 1988; NTP 1990; Anna *et al.* 1994; Bull *et al.* 2002) or where rats and mice were exposed by inhalation (Fukuda *et al.* 1983; Maltoni *et al.* 1986; Maltoni *et al.* 1988a). Trichloroethylene was carcinogenic in both rats and mice, including animals of both sexes, with tumors or evidence of cancer across the studies in both the liver and kidneys of the animals. I evaluated the studies themselves, as well as the reviews of these studies that were provided by both IARC (IARC 2012) and EPA (EPA 2012) and found that these studies support my overall conclusion that trichloroethylene exposure poses a cancer hazard.

37. I also reviewed a body of data and information related to trichloroethylene exposure and bladder cancer in humans since that relationship was part of the focus of my cancer hazard assessment. Scientists have reported an increased risk of bladder cancer with trichloroethylene exposure in four occupational cohort studies (Morgan *et al.* 1998; Raaschou-Nielsen *et al.* 2003; Zhao *et al.* 2005; Hansen *et al.* 2013) and in two case-control studies in workers (Pesch *et al.* 2000; Hadkhale *et al.* 2017). An additional case-control study in workers in France identified an increased risk of bladder cancer in workers that had been exposed to chlorinated solvents (*i.e.,* trichlorethylene, like perchloroethylene, is a chlorinated solvent;

Cordier *et al.* 1993); whether a worker in the study had been exposed to chlorinated solvents was adjudicated by a panel of industrial hygiene experts. Finally, a study in a population of US residents exposed to well water contaminated with trichloroethylene as well as tetrachlorethylene (perchloroethylene) and other solvents was reviewed (Mallin 1990); the authors reported an increased risk of bladder cancer in association with exposure to the contaminated water. The IARC monographs provide a detailed overview of many more epidemiological studies related to trichloroethylene exposure that also reported on risks of bladder cancer (IARC 2012; Tables 2.1, 2.2 and 2.3) but the authors of those studies did not find statistically significant increased risks of bladder cancer. Given that I was focused on hazard assessment, I reviewed these studies in the context of hazard which is the potential for harm. I weighed the human studies as a group in forming my opinions in this case, including the studies that failed to identify an association between trichloroethylene exposure and bladder cancer in humans. After my review of these human studies, I found that they support my overall conclusion that cancer, including specifically bladder cancer, is a human health hazard that has been associated with exposure to trichloroethylene in humans.

38. As already discussed above, all four of the chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, vinyl chloride, and benzene) can be metabolized in humans and that metabolism leads to production of reactive/toxic metabolites that are responsible for their adverse effects in biological systems. In the case of trichloroethylene specifically, the toxic metabolites are formed after oxidation of the chemical by liver enzymes (known as cytochrome P450 or "CYP" enzymes) or after conjugation by glutathione (as reviewed in EPA 2020b; Lash *et al.* 2014; Cichocki *et al.* 2016; Luo *et al.* 2018); the enzyme CYP2E1 has a specific role in the production of reactive trichloroethylene metabolites (*e.g.,* Luo *et al.* 2018), and this same enzyme is found in other tissues in the human body including the kidneys (*e.g.,* Liu and Baliga 2003; Moore *et al.* 2010; Abdelmegeed *et al.* 2017). As recently discussed in the literature (Lash 2024): *"Moreover, it has been established and accepted that virtually all of the adverse acute or chronic effects of TCE [trichloroethylene] exposure are dependent on its metabolism."*

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39. Like perchloroethylene, a characteristic of trichloroethylene relevant to this case, and to the hazard posed by the chemical, is its toxicokinetic profile. The toxicokinetic profile of trichloroethylene has been extensively reviewed (*e.g.,* Cichocki *et al.* 2016; EPA 2011; ATSDR 2019b; IARC 2012). More detail on the role of that metabolism of trichloroethylene may play as part of the mechanism underlying bladder cancer is discussed in Section VI.

40. Trichloroethylene is extensively absorbed after inhalation and oral exposures in humans (as reviewed in EPA 2011 and ATSDR 2019b; D'Souza *et al.* 1985; Astrand and Ovrum 1976; Monster *et al.* 1976; Fernandez *et al.* 1977; Perbellini *et al.* 1991; Yoshida *et al.* 1996; Bruning *et al.* 1998). After dermal or skin contact in humans, absorption of trichloroethylene in a liquid solution has been shown to occur as well (*e.g.,* Nakai *et al.* 1999; ATSDR 2019b; NTP 2015). Once trichloroethylene is absorbed into blood, it is distributed to all tissues in the body and can cross the blood-brain barrier as well as the placenta (as reviewed in EPA 2020b; Laham 1970; Cichocki *et al.* 2016). After oral absorption, trichloroethylene is metabolized in the liver on a first pass of blood through the body, while after inhalation exposures to trichloroethylene, due to the high blood/gas partition coefficient (comparable to anesthetic gases; ATSDR 2019b) most of the inhaled trichloroethylene will be rapidly absorbed and eventually undergo liver metabolism as well (as reviewed in ATSDR 2019b; Bartonicek 1962; Astrund and Ovrum 1976; Monster *et al.* 1976). The chemical accumulates in fatty tissues and in breast milk due to the lipophilicity[25] of the compound (Cichocki *et al.* 2016).

41. As a result of its accumulation in fat in the human body, the compound may stay in the body for an extended period of time after an exposure (EPA 2011; Monster *et al.* 1979b). As was the case with perchloroethylene exposure, accumulation of trichloroethylene in fat tissue is important in cases like the current case where daily exposures in water could occur and, as result of accumulation in fat, can lead to higher levels of trichloroethylene in the body over time (internal dose) than might be reflected by the level detected in water (external dose). This prolonged residence time in the body of trichloroethylene and its metabolites is reported as a "biological half-life" in the body; the term "biological half-life" is a measure of the amount of

[25] Lipophilicity means the chemical readily dissolves in fat or other lipid-rich tissues.

time it takes for 50% of the level of the chemical and its metabolites to be eliminated from the body. The half-life of trichloroethylene's toxic metabolites in the human body has been reported to be over 40 hours (Ikeda 1977; ATSDR[26]) which means that significant levels of the metabolites may still be found in cells and tissues before a new exposure may have occurred when exposures to trichloroethylene are a daily occurrence. Moreover, general principles of pharmacokinetics dictate that accumulation of the parent compound, trichloroethylene in adipose tissues can lead to continued metabolic conversion of the parent compound as it is released from adipose tissue*, i.e.,* ongoing exposure over time even days[27] after exposure has occurred. In the case of people exposed to the contaminated water at Camp Lejeune where many lived and worked on the base, exposure periods would be expected to episodic but occur more than once a day, meaning that accumulation of any trichloroethylene that would be absorbed into the body due to contact with the contaminated water would lead to the presence of some level of the chemical in the body at levels higher than might be predicted by only considering a measured level in the water and a single exposure.

42. As already mentioned, the metabolism of trichloroethylene in the body leads to the production of toxic metabolites that are responsible for the adverse effects the chemical has on biological systems, including the mechanisms that lead to cancer. Like perchloroethylene, the metabolism of trichloroethylene to toxic metabolites is saturable at higher levels of exposure (as reviewed in EPA 2011 and ATSDR 2019b; Feingold and Holaday 1977; Filser and Bolt 1979; Prout *et al.* 1985; Dekant *et al.* 1986b; Dallas *et al.* 1991; Lee *et al.* 2000a; Lee *et al.* 2000b; Cichocki *et al.* 2016), meaning that *more extensive metabolite formation occurs at low levels of exposure* as compared to higher exposure levels. This is important in the current case because the exposure experienced at Camp Lejeune may have been to lower daily levels as compared to exposure reported in epidemiological studies performed in worker populations in the past.

43. Once trichloroethylene's metabolites have been formed, by enzymes present in the liver or the kidneys, they are excreted through the kidneys into urine. The time that urine

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[26] https://www.atsdr.cdc.gov/csem/trichloroethylene/biological_fate.html#:~:text=The%20time%20between%20TCE%20inhalation,life%20%3D%20approximately%2052%20hours).

[27] The reported half-life of 41 hours that has been reported for trichloroethylene is close to 2 days.

remains in the body in humans can vary due to lifestyle factors or diseases; on average, adults generally void five to six times a day but no more than once after retiring to bed (Wrenn 1990[28]). This would mean that trichloroethylene metabolites could remain in contact with bladder tissue and urothelial cells throughout the bladder, kidney and ureters for at least four to five hours at a time. Specific reactive/toxic trichloroethylene metabolites will be discussed in Section VI of this report in connection with my discussion of the Hill considerations that are supportive of a cause-and-effect relationship between exposure to contaminated water at Camp Lejeune and bladder cancer in people that lived or worked on the base.

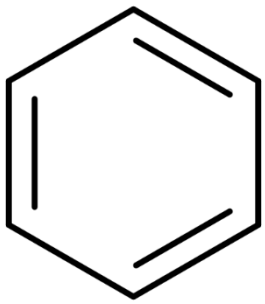
44. Based upon my education, training and experience, and considering the data and information identified and reviewed, it is my opinion to a reasonable degree of scientific certainty that it is at least as likely as not that exposure to trichloroethylene from contaminated water at Camp Lejeune was hazardous to human health generally, that exposure to the Camp LeJeune water contaminated with trichloroethylene specifically is hazardous to human health, and, further, that the human health hazard associated with exposure to Camp Lejeune water that contained trichloroethylene would include bladder cancer. This conclusion was reached based on: (1) my review of data collected in numerous toxicological studies (studies in cells and tissues, animals and in humans); (2) data showing that trichloroethylene was one of the four chemicals that contaminated the water at Camp Lejeune for decades; (3) consideration of the fact that the routes of exposure for humans that may have lived and worked at Camp Lejeune and were exposed to the contaminated water would have encompassed multiple relevant routes of exposure addressed in toxicological studies and human epidemiological studies (*i.e.,* ingestion of water, inhalation of volatilized trichloroethylene, and dermal contact); (4) consideration of the toxicokinetic profile of trichloroethylene that would impact human health hazard such as formation of reactive metabolites that have been linked to mechanisms of cancer (this information is discussed in Section VI of this report) and accumulation of the chemical and the metabolites in body tissues with repeated exposures; and (5) my training and experience in human health hazard assessment, including experience with trichloroethylene human health hazard and risk assessment.

[28] https://www.ncbi.nlm.nih.gov/books/NBK291/

C. Benzene

45. Benzene (C_6H_6; CAS Number 71-43-2) is also known by the chemical names of benzol, benzole, and cyclohexatriene. Its structure is shown below in Figure 3.[29]

Figure 3: Structure of Benzene



The human health hazards associated with exposure to benzene also are well-known and have been the subject of scientific reviews (*e.g.*, Wilbur *et al.* 2008; Barreto *et al.* 2009) as well as US government documents (*e.g.,* EPA 1998; ATSDR 2024a; NTP 2021c), and documents related to human health hazards associated with benzene authored by other authoritative bodies (*e.g.,* IARC 2012; IARC 2018; WHO 2019). Each of the government bodies and authoritative bodies who have produced consensus reviews related to perchloroethylene and human health hazards based their decisions on the same type of scientific evidence (peer-reviewed published studies) that I have relied upon in forming my opinions in this case and includes much of the same evidence I cite in this report. Of course, my research has the benefit of the availability of more recent supportive evidence. A review of all these documents shows that the principal adverse human health effects linked to exposure to benzene, regardless of the route of exposure, have included immunological and lymphoreticular effects reproductive effects, developmental effects, and cancer. Benzene has been classified as *"carcinogenic to humans"* by IARC (2012, 2018), as *"carcinogenic in humans by all routes of exposure"* by EPA (1998), and as *"a known human carcinogen"* by NTP (2021c).

46. Like most toxicologists would do, IARC, EPA, as well as NTP based its conclusions in part on evidence of cancer in experimental animals. As discussed in textbooks regarding human health hazard and risk assessment (*e.g.,* Faustman 2019), animal studies have

[29] https://pubchem.ncbi.nlm.nih.gov/compound/Benzene#section=Structures

been a key component of the hazard and risk assessment process for toxicologists for over forty years (Boorman *et al.* 1994). Such studies allow for the ethical examination of a range of doses (from very low to very high) in the same study and also allow for examination of changes at the tissue level (after sacrifice of the animals). In this case, also available for my review were the results from chronic benzene exposure studies where mice and rats. In the mouse studies, animals were administered the chemical by inhalation exposure (Snyder *et al.* 1980; Goldstein *et al.* 1982; Snyder *et al.* 1988; Cronkite *et al.* 1989; Farris *et al.* 1993; Li *et al.* 2006; Kawasaki *et al.* 2009) or by oral exposure (NTP 1986b; Maltoni *et al.* 1988b; Maltoni *et al.* 1989). In rats, the animals were exposed orally (Maltoni and Scarnato 1979; Maltoni *et al.* 1982; Maltoni *et al.* 1983; Maltoni *et al.* 1985; NTP 1986; Maltoni *et al.* 1988b; Maltoni *et al.* 1989) or by inhalation (Maltoni *et al.* 1983; Maltoni *et al.* 1985; Maltoni *et al.* 1989). Benzene was carcinogenic in both rats and mice, including animals of both sexes, with tumors or cancer reported across the studies in hematopoietic and lymphoid tissues, in particular. I evaluated these studies as well as the reviews that were provided in the most recent consensus review (IARC 2018) and found that these studies support my overall conclusion that benzene exposure poses a cancer hazard.

47. I also reviewed a body of data and information related to benzene exposure and cancer in humans since that relationship was the focus of my hazard assessment. There have be3en dozens of studies performed in humans that reported on an increased risk of leukemia and blood cancers in association with benzene exposures (reviewed in IARC 2012 and IARC 2018). In examining the benzene toxicology database for information relevant to the specific cancer hazard of bladder cancer, two human epidemiological studies not included in the IARC review documents were identified (Shala *et al.* 2023; Seyyedsalehi *et al.* 2024). Shala and colleagues (2023) reported that worker exposure to benzene was associated with an increased risk of bladder cancer. The authors performed the study to provide more accurate exposure assessment tools to address an increased risk of bladder cancer signal that had been reported previously in petroleum industry workers. Seyyedsalehi *et al.* (2024) performed a meta-analysis of 41 cohort and case-control studies and focused on relative risks of kidney, bladder, and urinary tract cancer overall. The authors reported: *"Our study found an association between occupational benzene exposure and kidney cancer and a dose-effect association between benzene exposure and bladder cancer."* The results of these recent studies suggest that the cancer hazard related to blood cancers, that is

well-accepted in association with benzene exposures in humans, may also apply to cancer of the urinary tract, including bladder cancer. Therefore, these more recent studies identify bladder cancer as a potential human health hazard related to benzene exposure as well. Although the human study data are limited, these new studies are supportive of my overall conclusions that cancer, including specifically bladder cancer, is a human health hazard that has been linked to benzene exposure in humans. The implications these data when assessing the cancer hazard of bladder cancer associated with exposure to contaminated water at Camp Lejeune is discussed when the issue of exposures to chemical mixtures and cancer hazard is discussed (discussed in Section VII).

48. As already discussed above, all four of the chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, vinyl chloride, and benzene) can be metabolized in humans and that metabolism leads to production of active metabolites that are responsible for their adverse effects in biological systems. In the case of benzene, the toxic metabolites are formed after oxidation of the chemical by liver enzymes (known as cytochrome P450 or "CYP" enzymes; reviewed in ATSDR 2024a; Henderson *et al.* 1989; Lindstrom *et al.* 1997; Ross 1996; Ross 2000), and these same enzymes also are found in other tissues in the human body including the bone marrow and the kidneys as well (ATSDR 2024a; Abdelmegeed *et al.* 2017). The enzyme CYP2E1 has a specific role in the production of reactive benzene metabolites (*e.g.,* Gut *et al.* 1996), and this same enzyme is found in other tissues in the human body including the kidneys (*e.g.,* Liu and Baliga 2003; Abdelmegeed *et al.* 2017).
More detail on the role of metabolism of benzene may play as part of the mechanism underlying bladder cancer is discussed in Section VI.

49. A characteristic of benzene, like all four of the chemicals in contaminated water at Camp Lejeune, that is relevant to this case, and to the hazard posed by the chemical, is its toxicokinetics. The toxicokinetic profile of benzene have been extensively reviewed (*e.g.,* EPA 1998; ATSDR 2024a; IARC 2012; IARC 2018). Authors have implicated the reactive metabolites formed in humans with toxicity in a variety of tissues and cells (*e.g.,* Ross *et al.* 1990; Valentine *et al.* 1996; Nebert *et al.* 2002; Huff 2007), including the bladder (*e.g.*, Xie *et al*.

2024). The toxic metabolites that are excreted into urine include phenol, hydroquinone, and catechol (*e.g.,* Rothman *et al.* 1998); all compounds known to be toxic (IARC 2018).

50. Benzene is extensively absorbed after inhalation and oral exposures in humans (reviewed in ATSDR 2024a; Parke and Williams 1953; Nomiyama and Nomiyama 1974; Sabourin *et al.* 1987; Trukall *et al.* 1988; Pekari *et al.* 1992; Laitinen *et al.* 1994; Lindstrom *et al.* 1994; Yu and Weisel 1996). After dermal or skin contact in humans, absorption of benzene in a liquid form has been shown to occur as well (reviewed in ATSDR 2024a; Lindstrom *et al.* 1994; Modjtahedi and Maibach 2008). Once benzene is absorbed into blood, it is distributed to all tissues in the body and can cross the blood-brain barrier as well as the placenta (as reviewed in ATSDR 2024a; Winek *et al.* 1967; Tauber 1970; Winek and Collum 1971; Pekari *et al.* 1992). The chemical also distributes to fatty tissues and into breast milk due to the lipophilicity[30] of the compound (as reviewed in ATSDR 2024a; Ghantous and Danielsson 1986; Zhang *et al.* 2020).

51. As already mentioned, the metabolism of benzene in the body leads to the production of toxic metabolites that are thought to be responsible for the adverse effects the chemical has on biological systems, including the mechanisms that lead to cancer. As is the case for perchloroethylene and trichloroethylene, the metabolism of benzene to toxic metabolites is saturable at higher levels of exposure (as reviewed in ATSDR 2024a; Sabourin *et al.* 1987; Knutsen *et al.* 2013a, 2013b), meaning *that more extensive metabolite formation occurs at low levels of exposure* as compared to higher exposure levels. This is important in the current case because the exposures experienced at Camp Lejeune may have been to lower daily levels as compared to exposure reported in epidemiological studies performed in worker populations in the past.

52. Once benzene's toxic metabolites have been formed, they are primarily excreted through the kidneys into urine (*e.g.,* Rothman *et al.* 1998). As described for perchloroethylene and trichloroethylene, once metabolites are excreted into urine, they contact tissues of the urinary system and even remain in the bladder for a period of time (hours, multiple times each day).

[30] Lipophilicity means the chemical readily dissolves in fat or other lipid-rich tissues.

Specific metabolites will be discussed in Section VII of this report as they relate to the likely mechanisms for carcinogenesis after exposure to contaminated water at Camp Lejeune.

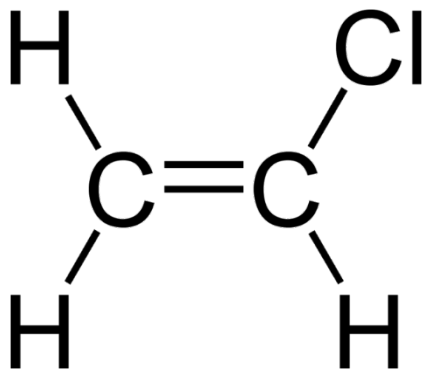
53. Based upon my education, training and experience, and considering the data and information identified and reviewed, it is my opinion to a reasonable degree of scientific certainty that it is at least as likely as not that exposure to benzene from contaminated water at Camp Lejeune was hazardous to human health generally, that exposure to the Camp Lejeune water contaminated with benzene specially is hazardous to human health, and, further, that the human health hazard could include the development of bladder cancer. This conclusion was reached based on: (1) review of data collected in numerous toxicological studies (studies in cells and tissues, animals and in humans); (2) data showing that benzene was one of the four chemicals that contaminated the water at Camp Lejeune for decades; (3) consideration of the fact that the routes of exposure for humans that may have lived and worked at Camp Lejeune and were exposed to the contaminated water would have encompassed multiple relevant routes of exposure addressed in toxicological studies and human epidemiological studies (*i.e.,* ingestion of water, inhalation of volatilized benzene, and dermal contact); (4) consideration of the toxicokinetic profile of benzene that would impact human health hazard such as formation of reactive metabolites that have been linked to mechanisms of cancer (this information is discussed in Section VI of this report); and (5) my training and experience in human health hazard assessment, including experience with benzene human health hazard and risk assessment.

D. Vinyl Chloride

54. Vinyl chloride (C_2H_3Cl; CAS Number 75-01-4) is also known by the chemical names of chloroethene and chloroethylene. Its structure is shown below in Figure 4.[31]

[31] https://pubchem.ncbi.nlm.nih.gov/compound/Vinyl-Chloride#section=2D-Structure

Figure 4: Structure of Vinyl Chloride



The human health hazards associated with exposure to vinyl chloride also are well-known and have been the subject of numerous US government documents (*e.g.,* EPA 1986a; EPA 2000a; ATSDR 2024b; NTP 2021d), and documents related to human health hazards associated with vinyl chloride authored by other authoritative bodies (*e.g.,* IARC 1997; IARC 2008; IARC 2012; Health Canada 2013). Each of the government bodies and authoritative bodies who have produced consensus reviews related to perchloroethylene and human health hazards based their decisions on the same type of scientific evidence (peer-reviewed published studies) that I have relied upon in forming my opinions in this case and includes much of the same evidence I cite in this report. Of course, my research has the benefit of the availability of more recent supportive evidence. A review of all these documents shows that the principal adverse human health effects linked to exposure to vinyl chloride, regardless of the route of exposure, have included immunological effects, liver effects, reproductive effects, developmental effects, and cancer. Vinyl chloride has been classified as *"carcinogenic to humans"* by IARC (2012), as *"carcinogenic in humans by all routes of exposure"* by EPA (2000), and as *"a known human carcinogen"* by NTP (2021c).

55. Vinyl chloride has not been identified as increasing the risk of bladder cancer in humans, yet a scientific consensus exists that exposure to vinyl chloride is a cancer hazard generally, and that it can cause certain types of cancer (ATSDR 2017a; Wagoner 1983; Kielhorn *et al.* 2000; Bolt 2005). The existence of a cancer hazard is well-accepted in association with vinyl chloride exposures in humans, with liver cancer being the focus of much human as well as

animal research (as reviewed in IARC 2012; Table 3.1; *e.g.,* Maltoni *et al.* 1981; Feron *et al.* 1981; Til *et al.* 1991). The implications of this association of vinyl chloride with a cancer hazard generally for assessing the cancer hazard of bladder cancer in this case is discussed when the issue of exposures chemical mixtures is discussed (discussed in Section VII).

56. As already discussed above, all four of the chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, vinyl chloride, and benzene) can be metabolized in humans and that metabolism leads to production of active metabolites that are responsible for their adverse effects in biological systems (as reviewed in IARC 2012; Gehring *et al.* 1978; Chiang *et al.* 1997). In the case of vinyl chloride, the toxic metabolites are formed after oxidation of the chemical by liver enzymes (known as cytochrome P450 or "CYP" enzymes; ATSDR 2024b; IARC 2012; Salmon 1976; Ivanetich *et al.* 1977; Sabadie et al. 1980), specifically involved is CYP2E1 (IARC 2012; Schindler *et al.* 2007; Hsieh *et al.* 2007), and these same enzymes also are found in other tissues in the human body including the kidneys (*e.g.,* Liu and Baliga 2003; Abdelmegeed *et al.* 2017).

57. A characteristic of vinyl chloride, like all four of the chemicals in contaminated water at Camp Lejeune, that is relevant to this case, and to the hazard posed by the chemical, is its toxicokinetics. The toxicokinetic profile of vinyl chloride have been extensively reviewed (*e.g.,* Bolt *et al.* 2005; EPA 2000a; ATSDR 2024b; IARC 2012).

58. Vinyl chloride is extensively absorbed after inhalation and oral exposures in humans (as reviewed in ATSDR 2024b; Withey 1976; Watanabe *et al.* 1976; Krajewski *et al.* 1980). Once vinyl chloride is absorbed into blood, it is distributed to all tissues in the body and can cross the blood-brain barrier as well as the placenta (as reviewed in ATDSR 2024b; Bolt *et al.* 1976; Watanabe *et al.* 1976; Buchter *et al.* 1977; Ungvary *et al.* 1978). Unlike perchloroethylene and tetrachloroethylene in particular, vinyl chloride and its metabolites do not appear to accumulate in fatty tissues with repeated exposures (Watanabe *et al.* 1978).

59. As already mentioned, the metabolism of vinyl chloride in the body leads to the production of toxic metabolites that are thought to be responsible for the adverse effects the

chemical has on biological systems, including the mechanisms that lead to cancer. As was reported for the other three chemicals that contaminated Camp Lejeune water, the metabolism of vinyl chloride to toxic metabolites is saturable (ATSDR 2024b; Bolt *et al.* 1977; Bolt 2005), meaning that *more extensive metabolite formation occurs at low levels of exposure* as compared to higher exposure levels. Again, this issue is important in the current case because the exposures experienced at Camp Lejeune could have been lower daily levels as compared to exposures reported in humans in the past.

60. Based upon my education, training and experience, and considering the data and information identified and reviewed, it is my opinion to a reasonable degree of scientific certainty that it is at least as likely as not that exposure to vinyl chloride from contaminated water at Camp Lejeune was hazardous to human health generally, that exposure to the Camp Lejeune water contaminated with vinyl chloride specially is hazardous to human health, and, further, that the human health hazard would include the development of cancer. This conclusion was reached based on: (1) review of data collected in numerous toxicological studies (studies in cells and tissues, animals and in humans); (2) data showing that vinyl chloride was one of the four chemicals that contaminated the water at Camp Lejeune for decades; (3) consideration of the fact that the routes of exposure for humans that may have lived and worked at Camp Lejeune and were exposed to the contaminated water would have encompassed multiple relevant routes of exposure addressed in toxicological studies and human epidemiological studies (*i.e.,* ingestion of water, inhalation of volatilized vinyl chloride, and dermal contact); (4) consideration of the toxicokinetic profile of vinyl chloride that would impact human health hazard such as formation of reactive metabolites that have been linked to mechanisms of cancer (this information is discussed in Section VI of this report); and (5) my training and experience in human health hazard assessment, including experience with vinyl chloride human health hazard and risk assessment.

E. Hazards Posed by Exposure to the Mixture of Chemical Contaminants in Camp Lejeune Water

61. In this case, a series of papers have been published in the peer-reviewed literature that reflect epidemiological studies performed in the Camp Lejeune population that reported cancer as a human health hazard (Bove *et al*. 2014a; Bove *et al.* 2014b; Ruckart *et al.* 2015; Bove *et al.* 2024a; Bove *et al.* 2024b).

62. Bove *et al.* (2014a) was a retrospective cohort mortality study conducted in populations of Marine and Naval personnel who began service during 1975-1985 and were stationed either at Camp Lejeune (exposure to contaminated water) or Camp Pendleton, California (no known exposure to contaminated water in the relevant time frame[32]). A similar retrospective cohort mortality study of civilian, full-time workers employed at Camp Lejeune during 1973–1985 and potentially exposed to contaminated drinking water also has been conducted, where the comparison cohort was composed of Camp Pendleton workers employed during 1973–1985 and unexposed to contaminated drinking water (Bove *et al.* 2014b). Given the fact that the exposed groups in these two studies were people that had actually ingested the mixture of chemicals in Camp Lejeune water, the results were of importance to my cancer hazard opinions. The authors of the studies reported elevated hazard ratios (HRs) for military personnel at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, as well as multiple myeloma, Hodgkin's lymphoma, and amyotrophic lateral sclerosis (ALS). Similarly, the civilian cohort exposed to the contaminated water at Camp Lejeune also exhibited elevated HRs for several causes of death including cancers of the kidney, rectum, and oral cavity, as well as leukemias, multiple myeloma, and Parkinson's disease. The third study related to cancer and exposure to Camp Lejeune water focused on the risk of breast cancer in men (Ruckart *et al.* 2015). In the case-control study, the results *"suggested possible associations between male breast cancer and being stationed at Camp Lejeune and cumulative exposure to PCE [perchloroethylene], DCE [dichloroethylene], and vinyl chloride, while TCE [trichloroethylene], PCE, DCE and vinyl chloride cumulative exposures showed possible associations with earlier age at onset of male breast cancer."* The results reported were not

[32] The authors indicated that Camp Pendleton was chosen as a comparator cohort based on the assumption that the Camp Pendleton cohort had not been exposed to the chemicals that contaminated the water at Camp Lejeune. If the Camp Pendleton cohort had been exposed to chemicals, however, the risk ratios reported in the studies comparing Camp Lejeune to Camp Pendleton would be expected to be underestimates of risk actually attributable to chemical exposures at Camp Lejeune.

conclusive, however, given the small number of cases in the exposed population. All three of these studies provide important evidence for the cancer hazard linked to the mixture of chemicals to which people were exposed at Camp Lejeune. All three of these studies corroborate the chemical-specific cancer hazard assessments I describe in this report. Yet, the fact that the two studies by Bove and colleagues (Bove *et al.* 2014a; Bove *et al.* 2014b) are mortality studies also should be considered in the context of the latency period of bladder cancer in humans. Given the fact that bladder cancer can have a latency period of decades and can be treated such that the life of affected individuals would be prolonged, it is possible that an endpoint other than mortality would have been needed to detect a causal association between exposure to contaminated water at Camp Lejeune and bladder cancer.

63. Two more recent studies have been published by Bove and colleagues (Bove *et al.* 2024a; Bove *et al.* 2024b) both relate to the Camp Lejeune population and their exposure to contaminated water. One study (Bove *et al.* 2024a) is a cohort mortality study among people who lived and worked at Camp Lejeune from as compared to people who lived and worked at Camp Pendleton, a base where there has been no exposure to contaminated water on base; this mortality study had an added 10-years of follow-up as compared to the 2014 mortality studies (Bove *et al.* 2014a; Bove *et al.* 2014b). The second 2024 study (Bove *et al.* 2024b) is a cohort cancer incidence study among people who lived and worked at Camp Lejeune, again as compared to people who lived and worked at Camp Pendleton (a similar but un-exposed population). In the mortality study, exposure to contaminated water at Camp Lejeune was again associated with elevated HR values for cancers of a variety of tissues. In the cancer incidence study, where the endpoint did not need to have led to death, the cancer data was based on diagnoses between 1996 and 2017 and was obtained from 54 different cancer registries. The authors reported increased risks of several cancers among the people exposed to the contaminated water at Camp Lejeune. These additional studies on the Camp Lejeune population corroborate the chemical-specific cancer hazard assessments I describe in my report. They also must be considered in light of the fact that bladder cancer can have a latency period of decades and can be treated such that the life of affected individuals would be prolonged. In his recent depositions[33], Dr. Bove has confirmed this would be at issue in this case given younger median

[33] Depositions of Frank J. Bove dated October 18 of 2024 at pages 59 and 127).

age in the cohort of marines, as compared to the average age at diagnosis for bladder cancer, meaning that the studies likely understated the incidence of bladder cancer.

64. When the epidemiological data on people that lived and worked at Camp LeJeune, as well as all of the other information reviewed and listed in this section of my report, is considered in light of my education, training, and experience, it is my opinion to a reasonable degree of scientific certainty that it is at least as likely as not that exposure to the chemicals that contaminated water at Camp Lejeune was hazardous to human health generally, and that the human health hazard would include the development of cancer. Although there was no increased risk of death due to bladder cancer in the studies by Bove *et al.* (2014a, 2014b, 2024a), the authors identified bladder cancer as one of the diseases with a relatively long survival rate and, as such, *"would require long-term follow-up to the Camp LeJeune cohort to fully evaluate the health impacts"* of the contaminated drinking water (Bove *et al.* 2014b). The results of the cancer incidence study (Bove *et al.* 2024b) reported an adjusted HR for bladder cancer 0f 1.09 for all types of bladder cancer and 1.09 for urothelial cell cancer of the bladder specifically; urothelial cell cancer cases were the most common type reported accounting for 97% of the cases. Thus, the studies conducted on people that lived and worked at Camp Lejeune add to the overall evidence that are supportive of my opinion that that exposure to perchloroethylene and trichloroethylene in the contaminated water at Camp Lejeune posed a bladder cancer hazard to humans.

VI. Hill Considerations and Support for a Causal Relationship Between Bladder Cancer and Exposure to Camp Lejeune Water

65. As discussed in Section V, the human health hazard that I have identified in association with all four chemicals that contaminated the water at Camp Lejeune (perchloroethylene, trichloroethylene, benzene, and vinyl chloride) was cancer generally, and in the case of perchloroethylene, trichloroethylene, and benzene, the human health hazard was identified as bladder cancer specifically. As mentioned in Section IV, to understand whether an identified hazard would be expected after an exposure, a toxicologist typically would look at what types of biological information are available that relate to the generally accepted ways that

cancer can develop in tissues such as the bladder. Biologic plausibility also is one of the Hill considerations that is considered when assessing cause-and-effect as part of any general causation assessment. There are two terms used by toxicologists to discuss biological information that explains what processes underly a type of adverse effect, *i.e.,* "mechanism of action" and "mode of action". Toxicologists refer to a "mode of action" as the sequence of major biochemical events that lead to an adverse response,[34] while "mechanism of action" provides details on the biological processes that underly a mode of action. In the current case, the mode of action for cancer, specifically human bladder cancer, was the focus of my assessment.

66. Also as discussed in Section IV, toxicology data and information also are an important part of any database of studies and may be adequate to support three additional Hill considerations: experiment, analogy, and coherence. Experiment is a consideration that involves determining if there are data that have been collected in studies in cells, tissues, or animals that can assist in analyzing cause-and-effect. An example of such studies would be genotoxicity studies as well as lifetime cancer studies in rodents. Analogy is a Hill consideration that describes looking at experience with similar chemicals in humans to see if the chemicals share biological properties that might be relevant to the mode of action for injury, in this case cancer. Coherence is a Hill consideration that addresses the question of whether the reported effect fits with the known pattern of disease. Data and information to support coherence also can be found in studies in cells, tissue, or animals.

67. Therefore, as a toxicologist in this case, I have formed opinions about these four Hill considerations based on the body of information I have reviewed that relate to exposure to the contaminated water at Camp Lejeune and cancer generally, as well as bladder cancer specifically.

A. Biologic Plausibility

68. In the case of the chemicals that contaminated the water at Camp Lejeune, consensus reviews have been performed in recent years by regulatory and authoritative bodies

[34] https://www.epa.gov/expobox/epa-expobox-terminology

such as the EPA, the ATSDR, the National Academy of Sciences (NAS), and IARC. Such reviews are based upon the current body of scientific knowledge as demonstrated in the peer-reviewed scientific literature and provide important sources of information related to the biological processes that are affected in mammalian cells and tissues (*in vitro* studies) as well as *in vivo* in animals and humans following exposure to the chemicals of interest in this case. The authors of these documents, documents that have undergone a peer-review process (internal and/or external), provide specific statements and conclusions that were reached about the underlying mechanisms or "mode of action" for induction of cancer in humans, including statements and conclusions regarding specific types of cancer. It is important to realize that data relevant to describing a mode of action for an adverse outcome observed in humans is elucidated most reliably by data collected either *in vitro* in cells and tissues or *in vivo* in animals because of the controls that can be put in place to allow for understanding the specific effects linked to a chemical exposure, controls that cannot be accounted for in most human epidemiological[35] studies. Just as in the field of toxicology generally, the consensus reviews related to cancer mode of action relied on studies in cells and tissues to understand how a chemical may be producing an adverse effect on human health such as cancer. In this case, although consensus opinions are relevant, I did not rely on the conclusions reached by the authoritative bodies that are stated in the consensus reviews, but instead used those documents as a starting point only, performing additional literature searches on the topic of mode of action for cancer associated with each of the four chemicals, and then evaluating studies and data in a weight-of-the-evidence assessment.

69. The exact molecular mechanism by which almost any chemical produces its effects, even in animals, is not known. Not knowing every detail about the molecular mechanism underlying trichloroethylene, perchloroethylene, benzene, or vinyl chloride exposure and carcinogenesis, however, does not mean that the available data fail to provide support for a likely cancer mode of action. In fact, we know some important things about all four of these chemicals, information that supports the biologic plausibility of the relationship between exposure to these chemicals and human bladder cancer. The mechanistic data discussed here provides highly plausible biological support for the hazard of human bladder cancer identified from human and

[35] Clinical studies to address cancer mode of action would be unethical to conduct for probable or known human carcinogens like perchloroethylene, trichloroethylene, benzene, and vinyl chloride.

animal studies and contributes to the overall information available for consideration when a causation analysis is performed by other experts in this litigation.

70. Before discussing the data and information for any of the four specific chemicals that relate to mode of action for cancer, it is important to understand some of the basic knowledge around the process of chemical carcinogenesis. As taught in textbooks of toxicology, chemical carcinogenesis is understood to involve a series of stages or steps and is referred to as "multistage carcinogenesis" (Klaunig and Wang 2019). Three defined stages have been identified: initiation, promotion, and progression. Initiation is a process where a stable heritable change in a cell. Promotion is the process whereby the heritable change in the cell leads to proliferation of the cell and/or a decrease in cell death, and the subsequent growth of preneoplastic lesions. Progression is the third stage in the multistage process whereby the preneoplastic lesion converts to the cellular phenotype of a tumor cell. In some references, a fourth stage, malignant transformation is described which is the process whereby the tumor cell, which could be benign, takes on a malignant phenotype. In cases where a chemical has actions to initiate, promote, and affect tumor progression as well, the chemicals are sometimes described as being "complete" carcinogens (Miller *et al.* 2017); such chemicals can, by themselves, result in cancer induction. Using that definition, all four of the chemicals (perchloroethylene, trichloroethylene, benzene, and vinyl chloride) at issue in the current case have been shown to be "complete" carcinogens based on studies in animals where exposures to those four chemicals alone were able to induce some form of cancer in an animal.

71. Also as discussed in toxicology textbooks, there are two basic types of chemical carcinogens, *i.e.,* substances that can result in cancer after exposure of cells or tissues to the chemical. The two broad types are genotoxic carcinogens and non-genotoxic carcinogens (Klaunig and Wang 2019). The term "genotoxic" refers to actual damage to the DNA in cells which can include single- and double-strand breaks to the DNA, point mutations, deletions, chromosomal aberrations, micronuclei formation, and even altered DNA repair. A non-genotoxic carcinogen is one that does not act by directly damaging DNA but instead leads to epigenetic changes in cells which are changes caused by modification of gene expression rather than alteration of the genetic code (mutation) itself. It is the general categories of genotoxic versus

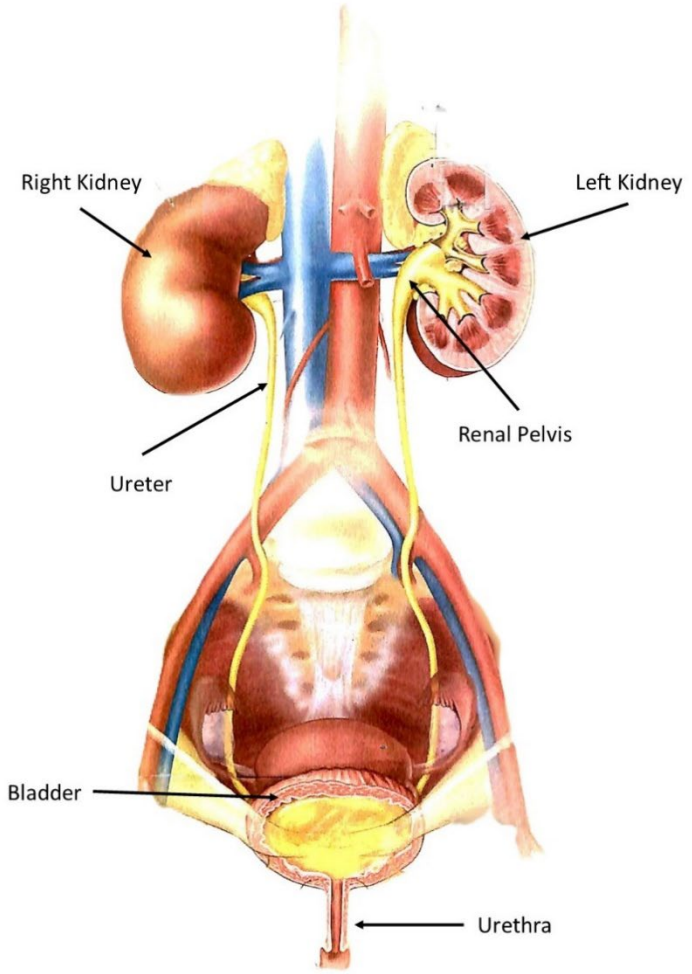
non-genotoxic carcinogens that are often referred to in scientific literature when the discussion centers around a likely mode of action for a particular carcinogenic chemical. This same distinction will be used to discuss the likely mode of action for the four chemicals at issue in this case (*i.e.,* perchloroethylene, trichloroethylene, benzene, and vinyl chloride).

72. As described in Section V, I have reviewed a variety of sources of information concerning the adverse effects on human health of the four chemicals that contaminated the water at Camp Lejeune (*i.e.,* perchloroethylene, trichloroethylene, benzene, and vinyl chloride). Those sources included consensus reviews, as well as literature identified in those documents, as well as through my own searches of the published literature, and my previous experience over the last 30 years working on projects where the toxicity of these four chemicals was at issue. My review identified important information related to the biological processes that are affected in mammalian cells and tissues (*in vitro* studies) as well as *in vivo* in animals following exposure to the four chemicals at issue in this case and were informative with respect to the likely cancer mode of action for each. I reviewed all of the information I identified for each chemical and applied a weight-of-the-evidence approach to reach my conclusions.

73. Important support for the biologic plausibility of the relationship between bladder cancer and exposure to any chemical, including perchloroethylene, trichloroethylene, or benzene, is based in the physiology of the human urinary system and how bladder tissue specifically can be exposed to carcinogenic substances. I have already discussed that, in the case of these three chemicals (perchloroethylene, trichloroethylene, and benzene), reactive/toxic metabolites are formed after exposure. Although these metabolites may be formed after circulation of the compounds in blood through the liver (perchloroethylene, trichloroethylene, and benzene), I also described how the kidney has the capacity to metabolize perchloroethylene and trichloroethylene and that the metabolites formed by glutathione conjugation in the kidney itself have been linked to a biologic mechanism for human kidney cancer (*e.g.,* IARC 2012; ATSDR 2019a; ATSDR 2019b; Luo *et al.* 2018). In the case of benzene, studies have shown that the toxic metabolites formed in humans are excreted into urine (*e.g.,* Rothman 1998). Once the reactive metabolites are present in, or formed in the kidney, basic human anatomy dictates that they may act locally in the kidney but also would be excreted into urine and pass from the kidney into the bladder.

74. The kidneys and the bladder are two distinct organ types in the human body that together with the renal pelvis, ureters, and urethra make up the urinary system (see Figure 5).

Figure 5: Anatomical Depiction of the Human Urinary System Components



Adapted from: https://nci-media.cancer.gov/pdq/media/images/649519.jpg

Like any organ system, specific types of cancer may develop in specific cell types within the organ. In the case of bladder cancer, urothelial cell cancer is the most frequent type.[36] Urothelial cell cancer has also been known as transitional cell carcinoma. Urothelial cells are the cells that line the inside of the bladder, but they also are found on the lining of the kidney, renal pelvis, ureters, and the urethra. Based on the anatomy of the urinary system alone, and because of being

[36] https://www.mayoclinic.org/diseases-conditions/bladder-cancer/symptoms-causes/syc-20356104

the cell type lining the tissues of the human urinary system (kidney, renal pelvis, ureter, bladder and urethra), urothelial cells are directly exposed to urine as well as any of the chemicals that might be excreted into urine.

75. As a result of the anatomy and physiology of the human urinary system, a key issue in my assessment of a likely mode of action for cancer of the urothelial cells that line the kidneys and bladder was to determine if the toxic metabolites of the four chemicals that are formed had the capacity to damage DNA, either directly through a genotoxic mode of action or that they caused epigenetic changes that have been lined to carcinogenesis (a non-genotoxic mode of action).

76. Scientific studies have shown that kidney toxicity associated with perchloroethylene exposure involves the following metabolic processes: (1) perchloroethylene conjugation with glutathione to form the compound S-(1,2,2-trichlorovinyl) glutathione (TCVG); (2) followed by processing of TCVG in the kidney to form S-(1,2,2-trichlorovinyl)-L-cysteine (TCVC); which is then followed by formation of the reactive metabolites (toxic metabolites) N-acetyl trichlorovinyl cysteine (NAcTCVC) and dichloroacetic acid (Lash and Parker 2001; Cichocki *et al.* 2016). These toxic metabolites are excreted into urine (as reviewed in EPA 2012; Lash *et al.* 2007; Cichocki *et al.* 2016; Luo *et al.* 2018), which means the entire human urinary system is exposed to the toxic perchloroethylene metabolites after they are excreted into urine. Once these perchloroethylene metabolites are in urine, studies have indicated the metabolites act to cause cancer through a genotoxic mode of action (reviewed in Cichocki *et al.* 2016; Dekant *et al.* 1986a; Vamvakas *et al*. 1989a; Vamvakas *et al.* 1989b; Dreessen *et al.* 2003).

77. Details on what specific metabolites are linked to adverse effects associated with trichloroethylene exposure, including carcinogenesis, also are found in the scientific literature. Scientific studies have elucidated the metabolic pathways for trichloroethylene, and the results of those studies have shown that kidney toxicity associated with trichloroethylene exposure involves trichloroethylene conjugation with glutathione to form the toxic metabolites S-dichlorovinyl-cysteine (DCVC); and S-dichlorovinyl-glutathione (DCVG) (Moore *et al.* 2010; Cichocki *et al.* 2016). These toxic metabolites are excreted into urine (as reviewed in EPA 2011;

Lash *et al.* 2007; Cichocki *et al.* 2016; Luo *et al.* 2018). This means that, as was the case for perchloroethylene, the entire urinary system would be exposed to the toxic/reactive metabolites that are excreted into urine. Once these trichloroethylene metabolites are in urine, studies have indicated the metabolites act through a genotoxic mode of action (reviewed in Cichocki *et al.* 2016; Jaffe *et al.* 1985; Dekant *et al.* 1986b; Vamvakas *et al.* 1988; Vamvakas *et al.* 1989b; Dreessen *et al.* 2003; Mally *et al.* 2006; Clay 2008). Then. as recently discussed in the literature (Lash 2024): *"Moreover, it has been established and accepted that virtually all of the adverse acute or chronic effects of TCE [trichloroethylene] exposure are dependent on its metabolism."*

78. As discussed in textbooks, chemicals that require metabolic activation to produce toxic effects in target cells (cells where cancer will develop) and that then result in genotoxic events are often acting at the initiation stage of carcinogenesis (Klaunig and Wang 2019). Therefore, after contact with the contaminated water at Camp Lejeune it would be expected that urothelial cells would be in direct contact with genotoxic compounds that have been linked to a biologically plausible mode of action for cancer (in the case of both perchloroethylene and trichloroethylene). Therefore, it is my opinion that when considering the known anatomy and function of the urinary system in humans, it is biologically plausible that toxic metabolites that have been linked to toxic effects in the kidney (*i.e.,* perchloroethylene and trichloroethylene) would also likely produce similar types of toxic effects in other parts of the urinary system in humans when cells come in contact with the toxic metabolites, *i.e.,* urothelial cells.

79. In the case of benzene, authors have implicated the reactive metabolites formed in humans with toxicity in a variety of tissues and cells (*e.g.,* Ross *et al.* 1990; Valentine *et al.* 1996; Nebert *et al.* 2002; Huff 2007), including the bladder *(e.g.,* Xie *et al.* 2024). The toxic metabolites that are excreted into urine after exposure to benzene include phenol, hydroquinone, and catechol; all of these metabolites are known to be toxic (IARC 2018). In fact, studies have shown that phenol (*e.g.,* Erexson *et al.* 1985; Barale *et al.* 1990; Yager *et al.* 1990; Anderson *et al*. 1995), hydroquinone (*e.g.,* Barale *et al.* 1990; Yager *et al.* 1990; Robertson *et al.* 1991; Anderson *et al*. 1995; Peng *et al.* 2013; Pereira *et al.* 2014; Luo *et al.* 2008), and catechol (*e.g.,* Yager *et al.* 1990; Robertson *et al.* 1991; Anderson *et al.* 1995; Barreto *et al.* 2009) are genotoxic. Therefore, as is mentioned with respect to genotoxic metabolites of

perchloroethylene and trichloroethylene that are excreted into urine, the benzene genotoxic metabolites also would be in direct contact with urothelial cells in the human urinary system once they are excreted into urine.

80. In the 2020 document entitled *Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro-) CASRN: 127-18-4* (EPA 2020a), the issue of the mode of action for tumor formation (carcinogenicity) of perchloroethylene in animals is discussed. Using a weight-of-the-evidence methodology, EPA concluded that metabolism is a key event in the mode of action for carcinogenicity and that metabolites of perchloroethylene are mutagenic. These conclusions reached by the EPA are supportive of my assessment of the likely mode of action for perchloroethylene to produce human urinary system cancer, specifically urothelial cell cancer.

81. In its 2012 review of perchloroethylene's cancer hazard for humans, IARC also provided a detailed discussion of the mechanism of carcinogenesis that they had identified from review of the peer-reviewed scientific literature (IARC 2012). It is important to realize that even though IARC is not a regulatory authority, its review process and all conclusions reflect the consensus decisions made by global experts in their field and without influence from industry or other parties with known conflicts of interest. In 2012, the panel of scientists that formed the Working Group at IARC concluded that reactive (toxic) metabolites formed in both the liver and kidney are genotoxic and their formation provides a plausible mechanistic basis for carcinogenesis in human tissues. IARC also pointed out that the metabolic pathways that have been characterized in humans as well as animals are qualitatively the same, even though humans and animals may differ in terms of the extent of metabolism and metabolite formation across species. These findings by IARC in 2012 also are supportive of my assessment of the likely mode of action for perchloroethylene-induced cancer of the urinary system.

82. In its 2019 review of the toxicity of perchloroethylene (ATSDR 2019a), ATSDR addressed the biological processes that underly mode of action for perchloroethylene as well (the compound is referred to by an alternative name, tetrachloroethylene, by ATSDR). Similar to discussion found in the EPA and IARC consensus review documents, ATSDR described the formation of reactive metabolites in liver and kidney as being important in terms of the

mechanism underlying toxic effects, even linking formation of those metabolites to toxic effects in liver and kidney tissue. ATSDR also points out (ATSDR 2012 at page 215) that the differences in toxicity in terms of dose-response seen in different animal species, such as rats versus mice, *"correlates well with differences in the metabolism of the compound."* Moreover, these conclusions by ATSDR are supportive of my assessment of the likely mode of action for perchloroethylene-induced cancer of the urinary system.

83. I identified several peer-reviewed papers of particular relevance to the discussion of biologic plausibility of the bladder cancer hazard linked to perchloroethylene and trichloroethylene exposure in humans. For example, Luo *et al*. (2018)[37] performed studies *in vivo* in mice that had been genetically modified to either exhibit no expression of the CYP2E1 gene (knockout of the gene) or to express the human form of the CYP2E1 gene, thus having the capability to produce human CYP2E1 in liver. The mice were exposed to perchloroethylene sub-acutely (intra-gastric administration of 100 mg perchloroethylene/kg bw/day for five days). Separate groups of genetically modified mice also were exposed to trichloroethylene, a single intra-gastric dose (600 mg trichloroethylene/kg bw) and those data will be discussed later in the section related to trichloroethylene mode of action. These researchers found that CYP metabolism played a critical role in generating metabolites that caused toxicity to both the liver and the kidney. They also summarized the knowledge in 2018 of the roles of oxidation of perchloroethylene as well as trichloroethylene in the liver and the action of glutathione conjugation as well (see page 490 of Luo *et al.* 2018).

> *"Both TCE and PCE are also metabolized by GSH conjugation via GSH-S-transferases (GSTs) to generate dichloro- or trichloro- GSH conjugates (DCVG/TCVG) (Lash et al., 2000). These conjugates can be further metabolized by hepatic or renal gamma glutamyl transferase and dipeptidase to form cysteine conjugates (S-(1, 2-dichlorovinyl)-cysteine [DCVC]/ S-(1, 2, 2-trichlorovinyl)-cysteine [TCVC]), and then are subject to n-acetylation to form NAcDCVC or NAcTCVC. These can be further bio-activated by a number of enzymes, including cysteine conjugate beta lyase, flavin monooxygenase, and CYPs, to form nephrotoxic metabolites such as reactive thiols (Volkel and Dekant, 1998)*

[37] This paper was part of the 2020 EPA review and the 2019 ATSDR review but was published after IARC's review.

and sulfoxides (Elfarra and Krause, 2007; Lash et al., 2001, 2003; Ripp et al., 1997; Werner et al., 1996).”

The issue of similarities overall in the formation of reactive metabolites during metabolism of perchloroethylene and trichloroethylene is further discussed with respect to the hazards posed by exposure to a mixture of chemicals in the contaminated water at Camp Lejeune.

84. As is the case for perchloroethylene, trichloroethylene consensus reviews also contain information related to the biological processes that are affected in mammalian cells and tissues (*in vitro* studies) as well as *in vivo* in animals that relate to a likely cancer mode of action for trichloroethylene (*e.g.,* EPA 2011; EPA 2020b; ATSDR 2019b; IARC 2012). I reviewed these documents as well and considered the individual pieces of scientific information and data discussed. The weight-of-the-evidence shows that the key initial event is metabolism of trichloroethylene in mammals, including humans, and that the formation of reactive metabolites leads to genotoxic events as well as initiation of non-genotoxic/epigenetic changes that then may lead to cancer. It is important to note that trichloroethylene and perchloroethylene share similarities in terms of the metabolic pathways involved. Both compounds form toxic and reactive metabolites due to actions of CYP2E1 and both also undergo glutathione conjugation in the liver as well as the kidney; these metabolic similarities are described in the consensus reviews. Therefore, the information in the consensus reviews is supportive of my assessment of the likely mode of action for human urinary system cancer after exposure to trichloroethylene.

85. Moreover, when considered together, the available data and information I have reviewed and considered provide for a biologically plausible mode of action for all three chemicals discussed here (perchloroethylene, trichloroethylene, and benzene) to cause bladder cancer in humans, providing evidence that fulfills the Hill consideration. The mode of action involves metabolism of each of these chemicals to reactive/toxic metabolites that are genotoxic in cells and tissues. The data and information also support extrapolation of this mode of action to human carcinogenesis that is linked to perchloroethylene, trichloroethylene, or benzene.

86. The last of the four chemicals that contaminated the Camp Lejeune water and that I evaluated with respect to a biologically plausible mode of action for human cancer was vinyl chloride. As described in Section V, consensus reviews related to vinyl chloride by EPA (EPA 2000a), ATSDR (ATSDR 2024), and IARC (IARC 2012) are available; these reviews were important sources of information related to the biological processes that are affected in mammalian cells and tissues (*in vitro* studies) as well as *in vivo* in animals following exposure to vinyl chloride and also were informative with respect to consensus opinions about the likely cancer mode of action for vinyl chloride. I reviewed these documents and considered the individual pieces of scientific information and data discussed. In the case of vinyl chloride, the toxic metabolites are formed after oxidation of the chemical by liver enzymes (known as cytochrome P450 or "CYP" enzymes; ATSDR 2024b; IARC 2012; Salmon 1976; Ivanetich *et al.* 1977; Sabadie *et al.* 1980; Chiang *et al.* 1997), specifically involved is CYP2E1 (IARC 2012d; Schindler *et al.* 2007; Hsieh *et al.* 2007), and this same enzymes also is found in other tissues in the human body including the kidneys (Liu and Baliga 2003; Abdelmegeed *et al.* 2017). The key toxic metabolite formed by the action of CYP2E1 is known as chloroethylene oxide and it has been shown to be genotoxic (Chiang *et al.* 1997). As a result, it is biologically plausible that formation of vinyl chloride's genotoxic metabolite by kidney CYP2E1 activity could result in excretion of the metabolite into urine and exposure of urothelial cells to another genotoxic entity.

87. Since the exposure to Camp Lejeune water involved exposure to a mixture of chemicals, I also addressed what the scientific information and data showed with respect to biologic plausibility of the relationship between the water at Camp Lejeune and human cancer. Considered together, the scientific data and information for all four of the chemicals that contaminated the water at Camp Lejeune support the biologic plausibility of the relationship between cancer hazard in humans and exposure to the chemicals in the contaminated water. All four chemicals are metabolized in the liver or other tissues in the body, including the kidney, to form toxic metabolites. The weight-of-the-evidence indicates the metabolites of all four chemicals are genotoxic. These characteristics, metabolism to reactive metabolites and the fact that the metabolites are genotoxic, are a similar feature of perchloroethylene, trichloroethylene,

benzene, and vinyl chloride in terms of the biologically plausible mode of action for cancer generally in humans.

88. In conclusion, when considered together, the scientific literature on the biological effects of trichloroethylene, perchloroethylene, and benzene provide sufficient evidence to show that exposure to these chemicals is associated with cellular changes that have been linked to carcinogenesis and that a plausible biological mechanism for carcinogenesis following exposure to perchloroethylene, trichloroethylene, and benzene more likely than not involves the steps of (1) formation of reactive metabolites in the liver and in kidneys; (2) excretion of the reactive metabolites into urine where they come in contact with cells that line the urinary system (urothelial cells); (4) interaction of the reactive and genotoxic metabolites with urothelial cells; and (5) initiation of genotoxic events that can lead to carcinogenicity in the bladder. The Hill consideration of biologic plausibility has, therefore, been fulfilled based on the weight-of-the-scientific evidence considered.

B. Experiment

89. "Experiment" as a Hill consideration relates to the ability to collect data to analyze the cause-and-effect relationship. In most causation assessments, the type of data relevant to this consideration are not human studies but are data collected in animals or cells that relate to the endpoint of concern and the exposure being considered. In this case, I focused on the Hill consideration of experiment with respect to support for the cause-and-effect relationship between bladder cancer and exposure to the three chemicals that I have concluded are associated with the cancer hazard of bladder cancer, *i.e.,* perchloroethylene, trichloroethylene, and benzene.

90. Studies relevant to this Hill consideration and perchloroethylene, trichloroethylene, and benzene exposure include the numerous cancer studies in animals that involved both oral and inhalation exposure to perchloroethylene (paragraph 26), cancer studies in animals that involved both oral and inhalation exposure to trichloroethylene (paragraph 36), and cancer studies in animals that involved both inhalation and oral exposure to benzene (paragraph 45). The studies described for all three chemicals share the characteristic of having been

designed to determine whether exposure to perchloroethylene, trichloroethylene, or benzene could cause some form of cancer in a mammal, in these cases rats as well as mice were tested in studies that approached the lifetime of the animals. As taught in textbooks, such studies in animals are a tool used routinely by regulatory authorities and scientists alike to provide inform on the likelihood that exposure to a chemical could cause cancer in humans (Klaunig and Wang 2019). These studies have the key advantages of being able to provide a direct comparison between exposed and non-exposed animals over the same time period and to deliver specific, controlled levels of exposure to the animal by a route of exposure that might be relevant for human hazard and risk assessment purposes. Since the animals are genetically the same in all study groups, a major source of variability in human epidemiological studies, inter-individual genetic differences, is now controlled for in the animals. Importantly, regulators often use the results of such cancer studies in animals to quantify risks to humans; the data is analyzed statistically and the number of tumors that are found when sacrificing the animals that have been exposed at various doses of the chemical are compared to the number of tumors found in unexposed animals. The statistical analysis applied results in defining the exposure-response relationship between the chemical and tumor formation that is referred to as either a "cancer slope factor" (for an oral animal study) or an "inhalation unit risk" value (for an inhalation study). Put more simply, the results of these animal studies allow a toxicologist to define the level of probability that might be associated with an exposure in humans. In the current case, the animal studies provide scientific evidence supporting a relationship between exposure to all three chemicals individually (perchloroethylene, trichloroethylene, and benzene) and an increased incidence of tumor formation (cancer) in animals.

91. As taught in textbooks of toxicology, genotoxicity studies are a common experimental system that was developed to assess the potential carcinogenicity of chemicals to which humans may be exposed (Klaunig and Wang 2019). Genotoxicity is defined as the potential of a substance to alter or damage the genetic material of a cell, its DNA. Mutagenicity is a specific type of genotoxicity where mutations in the genetic code are produced, Genotoxicity is the broader term and refers to mutations in DNA as well as other types of damage or alterations in the DNA of a cell. Genotoxicity testing is required around the world as part of regulatory submission for many different types of consumer products that contain chemicals

(*e.g.,* human drugs, medical devices, pesticides, industrial chemicals, food additives) and there are now standardized protocols that have been developed.[38] Such testing that was first developed in the 1970's (the Ames tests of mutagenicity) has the advantage of being short-term and inexpensive to conduct as compared to lifetime cancer bioassays in animals or even human epidemiology studies. Genotoxicity testing was initially used to predict whether or not a chemical could cause cancer but with the evolution of the science around carcinogenesis and the complexity of the process, genotoxicity testing data is used to provide insight into mechanisms of carcinogenicity.

92. In the case of perchloroethylene, trichloroethylene, and benzene, the genotoxicity studies discussed this report are examples of "experiment" as well. Genotoxicity studies also are discussed in the consensus review documents described in this report where a comprehensive listing is provided of the genotoxicity studies that have been performed on each of the three chemicals. A review of the most recent consensus review document relate to perchloroethylene (EPA 2020a) shows that the genotoxicity of both the parent compound and its reactive metabolites has been assessed (see Appendix J to the EPA 2020a document). My review of the published literature and the studies discussed in consensus reviews related to perchloroethylene reveals that perchloroethylene genotoxicity is linked to the presence of the compound's reactive metabolites (*i.e.,* Reichert *et al.* 1983; Vamvakas *et al.* 1989a; Vamvakas *et al.* 1989b; Vamvakas *et al.* 1989c; DeMarini *et al.* 1994; Dreesen *et al.* 2003; Irving and Elfarra 2013). In the case of trichloroethylene, the most recent consensus review document (EPA 2020b) shows that when the genotoxicity of the parent compound and its reactive metabolites are compared, it is when the reactive metabolites are tested that a positive signal for genotoxicity is reported (*e.g.,* Cichocki *et al.* 2016; Jaffe *et al.* 1985; Vamvakas *et al.* 1988a; Vamvakas *et al.* 1988b; Vamvakas *et al.* 1989b; Dreessen *et al.* 2003; Malley *et al.* 2006; Clay 2008). In the case of benzene, the genotoxicity database includes studies on both the parent compound and its metabolites and again shows that genotoxicity is linked to the presence of reactive benzene metabolites.

[38] https://www.oecd.org/en/publications/overview-on-genetic-toxicology-tgs_9789264274761-en.html

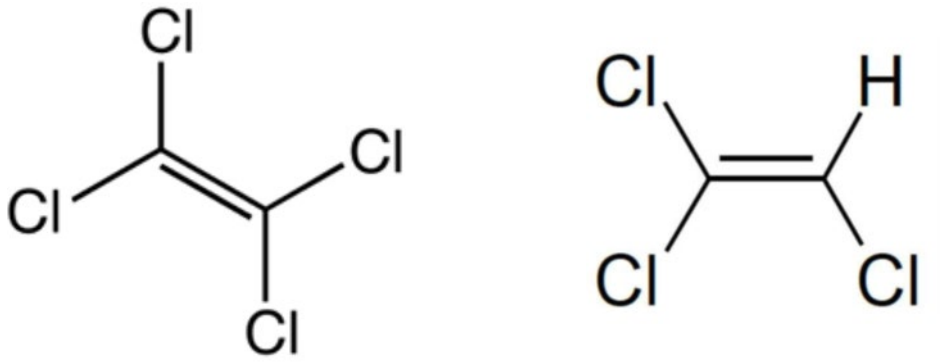
93. A third category of studies that are relevant to the Hill consideration of "experiment" are studies done in animals that had genetic alterations to their CYP liver enzyme systems, the enzymes that are known to metabolize a chemical to its reactive or toxic form. The animals are then exposed to the chemical to see if the toxicity in the animals is different or even prevented. One such study was discussed earlier (Luo *et al.* 2018) where role of the metabolism in the mode of action of perchloroethylene and trichloroethylene was assessed (Luo *et al.* 2018; paragraph 67). Luo *et al*. (2018) performed studies *in vivo* in mice that had been genetically modified to exhibit no expression of the CYP2E1 gene (knockout of the gene). The mice were exposed to perchloroethylene sub-acutely (intra-gastric administration of 100 mg perchloroethylene/kg bw/day for five days). Separate groups of genetically modified mice also were exposed to trichloroethylene, a single intra-gastric dose (600 mg trichloroethylene/kg bw). These researchers found that functional CYP metabolism played a critical, but not exclusive, role in generating metabolites that caused toxicity to both the liver and the kidney. This is expected given the fact that the scientific literature points to both CYP2E1 metabolism and glutathione conjugation as both being involved in perchloroethylene and trichloroethylene toxicity in both animals and in humans.

94. When considered together, the scientific literature describing genotoxicity studies and animal cancer studies where cells or animals were exposed to perchloroethylene, trichloroethylene, or benzene provide evidence that exposure to these chemicals produce cellular changes that have been linked to carcinogenesis in humans (genotoxicity studies) or that exposure *in vivo* in animals was consistently associated with an increased risk of tumor formation as compared to unexposed control groups of animals. These results are supportive of a cause-and-effect relationship between exposure to perchloroethylene, trichloroethylene, or benzene and cancer generally but when combined with the information related to the biologically plausible mechanism for bladder cancer already discussed, these studies can be used as part of a causation analysis to address the Hill consideration of experiment and support a cause-and-effect relationship between exposure to chemicals that contaminated the water at Camp Lejeune and bladder cancer in humans..

C. Analogy

95. "Analogy" is another of the nine Hill considerations and it also can be important when assessing cause-and-effect. As discussed by Dr. Hill: *"In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy."* In this case, consideration of the toxicology data related to structurally and chemically similar compounds would be relevant. In the case of the four chemicals at issue in this case, two of them, perchloroethylene and trichloroethylene, are structurally very similar, as shown in Figure 6 below:

Figure 6: Structural comparison of Perchloroethylene(left) and Trichloroethylene (right)



Inspection of Figure 6 shows that they differ only by the substitution of one hydrogen atom with a chlorine atom and even maintain the same two-carbon backbone: chemical formula of perchloroethylene is C_2Cl_4 while trichloroethylene is C_2HCl_3. Based on general principles of chemistry that are part of my education and training as a pharmacologist and toxicologist, these two chemicals would be expected to share certain biological properties such as similar pharmacokinetics and metabolism and even similar target organs of toxicity due to the presence of the multiple functional chlorine groups on a simple carbon backbone. As already discussed in some detail in this report, the pharmacokinetics and basic metabolism pathways are very similar for the two chemicals. In terms of target organs of toxicity, the two chemicals also have similarity, with both chemicals having toxic effects evidence in the liver and the kidney, and

both chemicals being linked to kidney cancer in humans via a similar genotoxic mode of action (EPA 2020a; EPA 2020b).

96. When considered together, the basic chemical and structural similarities of perchloroethylene and trichloroethylene as well as the scientific literature describing toxic effects in animals and in humans provide scientific support that fulfills the Hill consideration of analogy and provides support for a cause-and-effect relationship between exposure to these two chemicals in water at Camp Lejeune and bladder cancer in humans.

D. Coherence

97. The issue of "coherence" among the Hill considerations relates to whether the reported effect fits with the known pattern of disease. As described by Hill in 1965, data to support causation should not *"seriously conflict with the generally known facts of the natural history and biology of the disease."* My review of the human epidemiological data showing an association of exposure to perchloroethylene as well as trichloroethylene with bladder cancer in humans as well as the information and data discussed already with respect to mode of action and biologic plausibility of such a relationship are consistent with what is known about the epidemiology and etiology of bladder cancer.

98. For example, in a recent review paper (Halaseh *et al.* 2022) that describes the epidemiology and etiology of bladder cancer, the authors state with respect to etiology:

> *"The wall of the urinary bladder consists of four components: mucosa, submucosa, muscularis, and serosa. The typical urothelium of the mucosa is composed of a seven-cell thick layer of stratified, non-squamous, homogeneous cells with big umbrella cells on top. Tumors arising from the urothelial cells compromise most bladder cancer, with a rough estimation of 90%. They are formally known as transitional cell carcinoma. Other non-urothelial bladder malignancies that can arise include squamous cell carcinoma (SCC), small cell carcinoma, adenocarcinoma, and other tumors with mixed histology [11,12].* ***Due to urothelial direct exposure, the urothelial subtype is strongly related to exposure to chemicals,*** *such as workers exposed or tobacco smoking."*

With respect to epidemiology, the paper lists risk factors for bladder cancer that include aging, sex (males have in increased risk as compared to females), cigarette smoking, and occupational and environmental toxin exposures. Thus, the pattern of bladder cancer as a disease would include a finding that exposure to chemicals such as perchloroethylene, trichloroethylene, and benzene could increase the risk of the disease in humans. The discussion of bladder cancer etiology and epidemiology in this paper is a discussion of facts around the natural history and biology of the disease that are described by Hill (1965).

99. To fulfill the Hill consideration of coherence, I compared what is known about the toxic effects of perchloroethylene, trichloroethylene, and benzene generally with the information discussed in the scientific literature about how bladder cancer develops, what risk factors are known, as well as the basic biology of the human urinary system. As I describe in Sections V and VI of this report, the toxicological and toxicokinetic characteristics of perchloroethylene, trichloroethylene, and benzene provide support for a mode of action for bladder cancer that fits within current information on disease etiology and epidemiology. I would note that in the consensus review documents related to perchloroethylene and trichloroethylene by EPA, ATSDR, and IARC, as part of the epidemiological study evaluations, they point to the need to consider the risk factor of smoking, and they also describe the effect that age and sex can have on the epidemiological study conclusions that are drawn. In most of the epidemiology studies conducted that focused on exposure to perchloroethylene or trichloroethylene, they were performed in worker populations where the hypothesis being tested was whether certain types of workplace exposures to the chemicals increased the risk of cancer of many types, including the risk of bladder cancer in some cases (*e.g.,* EPA 2011; EPA 2012; EPA 2020a; EPA 2020b; IARC 2012). The studies performed in the population of people that lived and worked at Camp Lejeune (Bove *et al.* 2014a; Bove *et al.* 2014b; Ruckart *et al.* 2015) also considered the risk factors of smoking, age and sex when discussing their results. As a result, the Hill consideration of coherence is fulfilled.

VII. Chemical Mixtures and Carcinogenic Hazard and Risks in Exposed Populations

100. When considered together with general principles of toxicology, the available data relating to the cancer hazard of bladder cancer must be considered in light of the fact that human exposures at Camp Lejeune were to four different chemicals simultaneously in water, *i.e.,* a mixture, and that each of those four chemicals have been associated with the human health hazard of cancer.

101. The EPA has addressed the issue of risk assessment methods for chemical mixtures and has published guidance on how to perform a mixtures human health risk assessment for an exposed population (EPA 1986; EPA 2000b). EPA's guidance documents are found at https://www.epa.gov/risk/guidelines-health-risk-assessment-chemical-mixtures . The EPA website states:

> *"The 1986 Guidelines for the Health Risk Assessment of Chemical Mixtures represent the Agency's science policy and are a procedural guide for evaluating data on the health risks from exposures to chemical mixtures. The emphasis is on dose response and risk characterization. The principles and concepts put forth in the Guidelines remain in effect. However, in 2000, EPA issued a new document, Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (EPA/630/R-00/002 - August 2000). While the Guidelines describe broad principles and include few specific procedures, the 2000 guidance is a supplement that is intended to provide more detail on these principles and their applications."*

This EPA guidance outlines the methodology that I have used in the past, and also is generally used by other scientists in the field of human health risk assessment today, when estimating cancer risks in a population that has been exposed to a mixture of chemicals that are known to pose a cancer hazard (typically chemicals classified as probable or known human carcinogens by an authoritative body). The field of mixtures cancer risk assessment is an evolving field in science, but the EPA methodology is the generally accepted method used when considering risks to exposed populations when decisions need to be made in terms of preventing future adverse health effects in populations affected by chemical exposures.

102. In the current case, studies of humans exposed to the water at Camp Lejeune would be highly relevant to addressing concerns linked to exposure to a chemical mixture, not a single chemical. As already discussed in Section V.E., five such human epidemiological studies (*i.e.,* Bove *et al.* 2014a; Bove *et al.* 2014b; Ruckart *et al.* 2015; Bove *et al.* 2024a; Bove *et al.* 2024b) have been performed and these studies provide evidence for a human cancer hazard linked specifically to exposure to the water at Camp Lejeune that was a mixture of four toxic chemicals (perchloroethylene, trichloroethylene, benzene, and vinyl chloride).

103. All five human epidemiological studies that relate to the Camp Lejeune population and cancer were performed by scientists employed by the Agency for Toxic Substances and Disease Registry (ATSDR). Following their initial peer-reviewed publications in 2014 and 2015, the ATSDR published a separate type of analysis, a population human health risk assessment. The human health risk assessment is described as a "public health assessment" related to exposure to contaminated water at Camp Lejeune (ATSDR 2017a). In that document, the agency concluded that residents, workers, Marine and naval personnel, and Marines-in-training at Camp Lejeune had been exposed to contaminants in drinking water at levels that could have harmed their health as well as increasing their risk of cancer. The ATSDR found that exposures to water from the Hadnot Point Water System, the Tarawa Terrace Water System, and the Holcomb Boulevard Water System posed a risk to human health. Importantly, the ATSDR scientists recognized the issue of exposure to a mixture of chemicals that contaminated the water at Camp Lejeune. The agency acknowledged that the field is evolving and that there are limitations to use of the EPA methodology. They stated (page 43 of ATSDR 2017a):

> *"ATSDR notes that a limitation inherent in the public health assessment process is that* ***scientists do not have a complete understanding of how simultaneous exposures to several environmental contaminants influence the magnitude of health effects****. This is a limitation of the evolving field of mixtures assessments."*

Even though they acknowledged limitations in the methodology for mixtures risk assessment, the ATSDR Public Health Assessment document (ATSDR 2017a) quantified the risk of cancer attributed to exposure to the mixture of chemicals in Camp Lejeune water using existing EPA guidance for cancer risk assessment of chemical mixtures (EPA 1986; EPA 2000b); this

approach is consistent with actions taken by scientists in the US at other sites of environmental contamination.

104. In their risk assessment, the scientists at the ATSDR considered exposure through direct ingestion of drinking water, dermal contact/exposure to water, as well as inhalation of the volatile organic chemicals found in the water as a result of activities such as showering[39] and bathing. In their exposure assessment, they assumed that the exposure was for a period of three years while living or working on the base. The ATSDR found that there was an increased risk of cancer in people exposed to the contaminated water at Camp Lejeune that exceeded the acceptable risk levels typically applied in EPA cancer risk assessments for populations exposed to chemical contaminants in the environment; excess cancer risk was found to be more than 1 in 10,000 in most cases across all ages of individuals studied (children; workers that lived off the base as well as Marines that trained on the case; Figure 9 of ATSDR 2017a) and more than 1 in 100,000 in other instances (Figure 10 of ATSDR 2017a). Given that available data had shown that exposure to a mixture of the four chemical water contaminants was likely, and that the four chemicals at issue shared some important properties (*i.e.,* all were volatile organic chemicals; all have to be absorbed and metabolized to reactive metabolites; and that the metabolites formed likely are carcinogenic due to a genotoxic mode of action in some tissues), it is my opinion that the use of mixtures risk assessment approach was scientifically valid.

105. A second mixtures cancer risk assessment for humans exposed to contaminated drinking water at Camp Lejeune was recently published in the peer-reviewed literature (Rosenfeld *et al.* 2024). The authors used a mixtures risk assessment method very similar to the one that had been used by the ATSDR in 2017. The risk assessment also considered exposure through ingestion (oral), dermal and inhalation exposure pathways using exposure assessment data provided in the ATSDR 2017 Public Health Assessment document (ATSDR 2017a) and applying the ATSDR's 2017 data in exposure assessments based on EPA guidance related to human health risk assessments (EPA 1989; EPA 2004). The authors reported that trichlorethylene and vinyl chloride were "the risk drivers" in their assessment in terms of cancer

[39] Studies have shown the heating of the water during showering and bathing results in exposure to volatile organic compounds (*e.g.,* Chen *et al.* 2003; Franco *et al.* 2007).

hazard while benzene and perchloroethylene contributed to the cumulative cancer risk for Marines that lived and worked at Camp Lejeune from 1953 to 1987. Importantly, they found:

> *"VC [vinyl chloride] and TCE [trichloroethylene] exposure* ***for periods as short as 1 month can exceed a 1 in a million de minimis cancer risk value.*** *" [****emphasis*** *added]*

This statement about risk in the population even with consideration of only a one-month exposure period is important because as discussed in the ATSDR (2017a) public health assessment, many of the people that lived and worked on the base likely were exposed for years, not a single month (see page 20 in ATSDR 2017a). Importantly, the assessment provided by Rosenfeld and colleagues (2024) confirms the cancer hazard and even the general level of risk that was estimated for the population and that ATSDR had identified in their 2017 Public Health Assessment.

106. In 2024, the EPA's guidance on risk assessment for chemical mixtures, including methods to be used in cancer risk assessment, can be found at https://www.epa.gov/risk/guidelines-health-risk-assessment-chemical-mixtures [accessed November 15, 2024]. The EPA website states:

> *"The 1986 Guidelines for the Health Risk Assessment of Chemical Mixtures represent the Agency's science policy and are a procedural guide for evaluating data on the health risks from exposures to chemical mixtures. The emphasis is on dose response and risk characterization. The principles and concepts put forth in the Guidelines remain in effect. However, in 2000, EPA issued a new document, Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (EPA/630/R-00/002 - August 2000). While the Guidelines describe broad principles and include few specific procedures, the 2000 guidance is a supplement that is intended to provide more detail on these principles and their applications."*

Therefore, given that EPA today is still proposing their mixtures guidance as appropriate for use when performing a mixtures chemical risk assessment where cancer is the endpoint of concern, I performed a mixtures health risk assessment based on available exposure data for Camp Lejeune as well.

107. In designing my mixtures risk assessment approach, I decided to focus first on the oral ingestion pathway for perchloroethylene, trichloroethylene, benzene, and vinyl chloride that would be associated with drinking water on base. This was done because if the cancer risk level for the Camp Lejeune population is elevated over the accepted *de minimis* of one in a million-cancer risk level ($1x10^{-6}$) for a population based only on consideration of that one known exposure pathway, then adding consideration of the additional exposure pathways (*i.e.,* inhalation and dermal) would only increase the estimated risk further and likely would not change the conclusion that the level of risk in the population. I also chose to initially determine the impact of oral ingestion of the mixture of toxic chemicals found in the Camp Lejeune water. given the fact that dermal exposures to perchloroethylene, trichloroethylene, benzene, and vinyl chloride had already been shown to be minor in terms of their contribution to overall levels of exposure to the chemicals (Rosenfeld *et al.* 2024; ATSDR 2017a), and the fact that the modeling of inhalation exposures is inherently more uncertain based on exposure assumptions that must be made in cases where inhalation is attributed to showering and bathing in contaminated water (see equations listed on page 124 of Rosenfeld *et al.* 2024).

108. In Appendix D to this report, a spreadsheet showing the details of my risk calculations is provided. The equation I used to calculate an oral exposure dose is the one used in Rosenfeld *et al.* (2015) and recommended by EPA for cancer risk assessment (EPA 200a) but with use of some different input data for certain variables that I chose based on my experience and training in performing a population risk assessment. Based upon my training and experience in toxicology and risk assessment, the assumptions I applied were both appropriate and reasonable. The equation is:

$$\text{Dose (mg/kg-day)} = \frac{\text{water (mg/L) x Intake rate (L/day) x 365 (days/year) x 3 years}}{\text{(365 days/year x 78 years) x 70 kg bw}}$$

First, although there were children living on base that were exposed to the contaminated water at Camp Lejeune, I only assumed adult exposures. I assumed a 70 kg body weight, which is a

standard adult body weight used by risk assessors[40], to account for both males and females in the population and both military personnel and civilian workers. I assumed either 4 L per day or 8 L per day of water ingestion and then input either the mean level of a chemical contaminant from the Tarawa Terrace System (1975-1985), the mean level of a chemical contaminant from the Hadnot Point System (1975-1985) or the mean level of a chemical contaminant in water from those two systems combined (the average of the values from both water systems). The levels of chemical contaminants in water are found in Tables 1a and 1b of ATSDR (2017a). I chose 4 Lor 8 L of intake per day based on estimates used in ATSDR (2017a) where adults were estimated to be drinking from 3-4 L of water per day. The 8 L ingestion rate was chosen based on statements in Bove *et al.* (2014a) that combining the 4 L per day water ingestion rate with dermal and inhalation exposures from showering twice a day could result in a consumption equivalent of up to 8 liters of drinking water per day. The calculated dose of each chemical is then multiplied by the unique cancer slope factor (CSF) that has been determined for each of the four chemicals; the description of what a cancer slope factor is can be found above in paragraph 90; it is the value derived from results of an animal or human study that defines the exposure-response relationship between the chemical and tumor formation. Thus, the estimates of cancer risk for each chemical as shown in Appendix D result from the following general equation:

Cancer Risk = Dose (exposure) x CSF (for oral exposure)

In a mixtures risk assessment, the individual cancer risk values would be added together to arrive at an estimate of oral cancer risk due to exposure to the mixture.

109. The estimates of oral cancer risk for each chemical were added together to arrive at an overall estimate of oral cancer risk for the mixture. My estimates are shown below in Table 1.

[40] The 70 kg body weight was the standard value used by EPA that was used up until 2015. (https://www.epa.gov/sites/default/files/2015-10/documents/human-health-2015-update-factsheet.pdf). Given this case involves historical exposures, I felt this value was appropriate.

TABLE 1 Estimates of Cancer Risk Due to Exposure to Contaminated Water at Camp Lejeune		
Water System	**Ingestion Rate Assumed[1] (L water/day)**	**Estimated Oral Cancer Risk**
Tarawa Terrace System	4	1.01 E-5
	8	2.03 E-5
Hadnot Point System	4	7.49 E-5
	8	1.5 E-4
Combined Systems	4	4.28 E-5
	8	8.57 E-5
[1] The ingestion rates of 4 L or 8 L were chosen based on reasonable assumptions as described in paragraph 108.		

An estimated oral cancer risk value such as are found in Table 1 are an expression of the likelihood that cancer might occur in the population and be attributed to exposure to the contaminated Camp Lejeune water. Inspection of the estimates of cancer risk for the Camp Lejeune adult population shows that based only on consideration of oral ingestion, the cancer risk levels are well above the *de minimis* level, *i.e.,* one excess case of cancer in a million people in the population, typically used to identify when the level of risk needs to be mitigated (Castorina and Woodruff 2003). In fact, the cancer risk levels estimated here for one route of exposure (oral only; using a 4 L per day intake rate) exceeded one in 100,000 in all cases. In the case where the intake rate of Hadnot Point water was estimated to be 8 L per day in order to account for other known routes of exposure to the contaminated water (dermal and inhalation) the cancer risk is estimated to be greater than 1 in 10,000. Based on my experience in cancer risk assessment for populations exposed to chemicals due to environmental contamination, the levels of risk are unacceptable and would require interventions to prevent future exposures and mitigate harm to the population.

110. In the risk assessment I performed here (Appendix D), as well as in the risk assessments performed by ATSDR (2017a) and by Rosenfeld *et al.* (2024), I employed the

cancer slope factors developed as part of regulatory assessments by the EPA and their IRIS[41] program. The IRIS program is described by EPA[42] as follows:

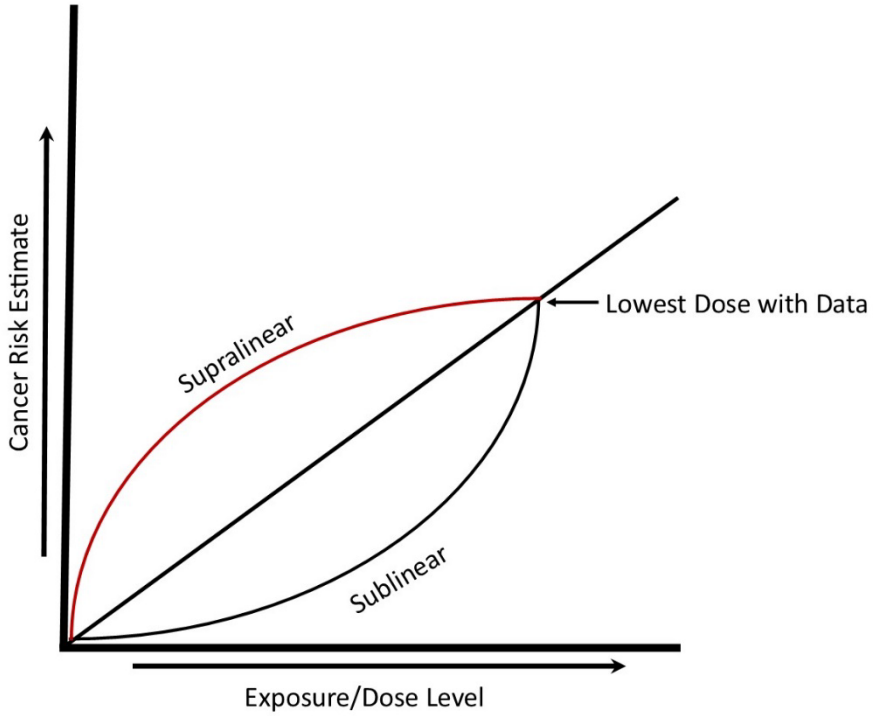
> *" EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment. Each IRIS assessment can cover a chemical, a group of related chemicals, or a complex mixture. IRIS assessments are an important source of toxicity information used by EPA, state and local health agencies, other federal agencies, and international health organizations."*

IRIS has performed cancer risk assessments for perchloroethylene, trichloroethylene, benzene, and vinyl chloride[43] and published oral cancer slope factors for each chemical. A review of the IRIS website shows that the cancer slope factors (CSFs) for each of the four chemicals were derived based on use of linear extrapolation methods.

111. A "linear extrapolation" means that the scientist has estimated a risk that might be associated with exposure to low levels of carcinogenic substances present in the environment by linear extrapolation from higher exposure levels at which risks can be estimated directly (Krewski *et al.* 1991). This is important because the assumption is made that there is a linear relationship between an exposure level and the risk estimate even though there are situations where this may not be the case. An example relevant to this case is when there is a saturation of the metabolic process that results in formation of the ultimate carcinogen. This was discussed above with respect to all four of the chemicals that contaminated the water at Camp Lejeune and it means that more extensive toxic metabolite formation occurs with all four chemicals at low levels of exposure as compared to higher exposure levels. This is referred to as a "supralinear" relationship and can be depicted as shown below in Figure 7. By using a linear method for extrapolation in derivation of the CDFs for each of the four chemicals that contaminated the water at Camp Lejeune, use of these CDF values in a cancer risk assessment my actually underestimate cancer risk levels when exposure is to low doses that are not affected by saturation of the enzymes that activate the chemicals.

[41] IRIS is the acronym for the *Integrated Risk Information System* at EPA (https://www.epa.gov/iris).
[42] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system
[43] https://iris.epa.gov/AtoZ/?list_type=alpha

Figure 7: Depiction of supralinear extrapolation of cancer risk estimates



112. Considered together, the cancer risk assessments that have been performed by others and by myself are consistent in showing that people that lived or worked at Camp Lejeune were exposed to a hazard to human health generally, and specifically to a cancer hazard. This risk would include a risk of bladder cancer given the fact that, based on my assessment of cancer hazard, three of the four chemicals contained in the contaminated water at Camp Lejeune have been linked to that form of cancer in humans.

VIII. Cancer Hazards in Humans: How Inter-Individual Differences in the Human Population Can Affect the Susceptibility of Certain Individuals to Cancer

113. It is well-established that there are differences between humans in a population that can affect their response to a chemical exposure (Faustman 2019[44]). They are sometimes referred to as "inter-individual" differences. Inter-individual differences can be due to readily identifiable characteristics such as age, sex, and health status, but also important are things such as genetics, diet and lifestyle, and body composition (percentage fat versus lean mass). In some cases, inter-individual differences in toxic responses to a chemical may be a function of how many times a person may have been exposed to that chemical, or similar chemicals, in the past.

114. In human risk assessment guidance and guidance applied to chemical-specific human health assessments as well, the scientific literature, regulatory agencies and authoritative bodies will refer to the issue of inter-individual differences and discuss how it may impact hazard and risk assessment using the term "susceptibility factors" (*e.g.,* Perera 1996; Sexton 1997; Faustman 2019; Varshavsky *et al.* 2023; EPA 2011; EPA 2012; EPA 2020a; EPA 2020b; IARC 2012; IARC 2018). The same type of factors that are considered inter-individual differences are discussed as susceptibility factors (*i.e.,* age, sex, body composition, genetics, health status). The importance of such differences between exposed people in a population on toxic effects or responses that are associated with a chemical exposure explains why it is that not everyone in a population that is exposed to a similar level of a chemical will experience an adverse effect (Varshavsky *et al.* 2023). Based on these known principles of science that affect chemical toxicity potential, not everyone exposed to the contaminated water at Camp Lejeune would be expected to develop cancer, or even the same type of cancer. Below is a description of the conclusions relevant to individual susceptibility that have been supported by scientific data, including discussion of conclusions drawn by scientists and authoritative bodies related to perchloroethylene, trichlorethylene, benzene, and vinyl chloride. Consideration of the evidence in this case indicates that inter-individual differences related to toxic responses elicited after exposure to different individuals among the human population would be expected to occur in the case of all four of the chemicals that contaminated the water at Camp Lejeune.

[44] Faustman, E.M. 2019 Risk assessment. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons, 9th Edition*. McGraw-Hill: New York, NY. Chapter 4.

115. In a recent peer-reviewed publication (Varshavsky *et al.* 2023), the authors describe the intrinsic and extrinsic factors that influence human variability in terms of chemical exposure-response relationships and *"heighten the susceptibility to toxic environmental exposures in human health risk assessment."* Figure 1 in the paper (shown below) summarizes some of the factors that they authors refer to as either "intrinsic" or "extrinsic" factors.

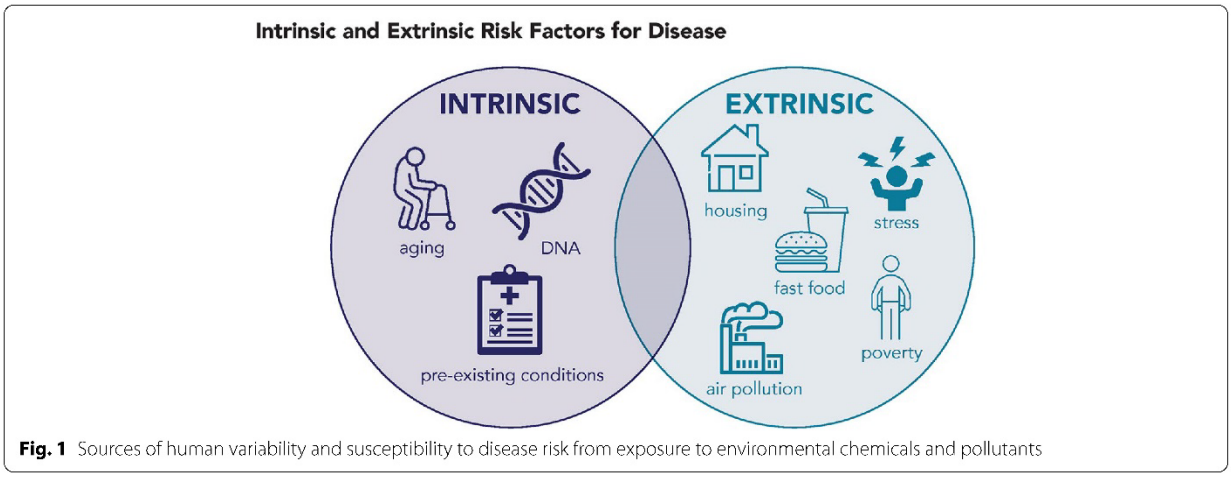


Fig. 1 Sources of human variability and susceptibility to disease risk from exposure to environmental chemicals and pollutants

As mentioned, these factors may interact such that their impact is additive or even synergistic in terms of impacting the level of risk that might be seen as compared to persons that do not exhibit susceptibility factors. An important concept described in the paper is the fact that extrinsic and intrinsic factors can interact to increase the risk of experiencing an adverse health outcome in association with any exposure, and that current risk assessment methods do not account for such interactions. Clearly, the issue of inter-individual susceptibility factors is an important consideration whenever the risks to a population are characterized and when conclusions may need to be applied to any individuals within a population.

116. An example of a general description of the issue of susceptible populations also is found within consensus reviews with respect to the individual chemicals at issue in this case. For example, the recent EPA assessment of perchloroethylene (EPA 2020a). EPA has stated:

> *"Factors affecting susceptibility examined in the available studies on PCE include lifestage, biological sex, genetic polymorphisms, race/ethnicity, preexisting health status, lifestyle factors, and nutrition status.* ***Individuals exhibiting any of these factors can be considered part of a susceptible subpopulation****." [page 335 of EPA 2020a]*

In the ATSDR Public Health Assessment in 2017 (ATSDR 2017a), the scientists recognized that age was an important susceptibility factor that needed to be considered. In fact, EPA has issued guidance on the susceptibility of children to certain types of chemical exposures (EPA 2005[45]) and provides guidance as to how to account for that susceptibility when performing a cancer risk assessment for chemicals where data are available to show that age affects cancer hazard. In the case of the chemicals that contaminated the water at Camp Lejeune, both trichloroethylene and vinyl chloride are recognized as posing a unique hazard to health during early life exposures (ATSDR 2017a; EPA 2000a; Chiu *et al.* 2013).

117. Another well-recognized inter-individual difference that might affect the cancer response in humans to exposure to the chemicals that contaminated the water at Camp Lejeune would be body composition. As discussed in Section V of this report, perchloroethylene and trichloroethylene, in particular, may accumulate in fat in humans (Cichocki *et al.* 2016; and as reviewed in EPA 2011; EPA 2020a; EPA 2012; EPA 2020b). As EPA stated in its evaluation of perchloroethylene (EPA 2020a): *"Long residence time in adipose tissue can result in increasing body burden with continuous or repeated exposures."* [see page 287 of EPA 2020a] The issue of fatty tissue body burden is important in cases like the current case where daily exposures in water could occur and lead to higher levels of perchloroethylene or tetrachloroethylene in the body than might be reflected by a level detected at any one point in time in water.

118. Genetic differences in the human population are an inter-individual difference among humans that has been specifically discussed in the peer-reviewed literature as it relates to chemical risk assessment (*e.g.,* Varshavsky *et al.* 2023), but also by authoritative bodies and regulatory authorities as a susceptibility factor for cancer related to exposure to all four chemicals at issue in this case (perchloroethylene, trichloroethylene, benzene, and vinyl chloride). The genetic issues relate in large part to the existence of polymorphisms[46] in the key enzymes that metabolize these four volatile organic compounds. As already discussed, all four of these chemicals are metabolized by a liver CYP enzyme known as CYP2E1, which is an enzyme

[45] US Environmental Protection Agency. 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F, March 2005.
[46] A genetic polymorphism is generated by mutations in the genes that encode for an enzyme and then can lead to a decreased, increased, or even no enzyme expression or activity in a cell or tissue.

where polymorphisms have been well-documented (*e.g.,* Hildesheim *et al.* 1997; Hu *et al.* 1997; Neafsey *et al.* 2009; Wang *et al.* 2017; Ijaz *et al.* 2024), with the presence of CYP2E1 polymorphisms even being linked to an increased risk of cancer (Hildesheim *et al.* 1997). The ATSDR (ATSDR 2019a) described genetic differences in metabolism of perchloroethylene in certain ethnic populations (which could be due to the existence of a common polymorphism), as well as the existence of polymorphisms in key enzymes that produce reactive metabolites. In the case of trichloroethylene, IARC (2012) discussed the fact that metabolism of the chemical to its reactive (toxic) metabolites occurs through enzymes where genetic polymorphisms exist that affect the extent and rate of metabolism of trichloroethylene. Similar discussion by ATSDR (ATSDR 2024b) is found as it pertains to the existence of genetic polymorphisms of the enzymes that lead to formation of vinyl chloride's toxic metabolites, as well as benzene (ATSDR 2024a). Any differences in the rate and extent of metabolism of these four chemicals are relevant to the discussion of cancer hazard at Camp Lejeune and would be one issue to consider when discussing the likelihood that cancer may or may not be seen in any one individual in the population.

119. Sex-related differences and the effects that sex may have on the toxic responses that result from human exposure to benzene, vinyl chloride, perchloroethylene, and trichloroethylene also is a consideration. Higher body fat content in women versus men is well-known to exist and body fat has already been mentioned. Studies in humans exposed to benzene have found that elimination of the chemical in women is slower than it is in men (Sato *et al.* 1975; Poli *et al.* 2022; ATSDR 2024a) and slower elimination would mean greater opportunity for exposure to toxic metabolites and greater hazard posed to women as compared to men. Sex-related differences also have been discussed with respect to the greater susceptibility of males to perchloroethylene-induced kidney toxicity as compared to females (*e.g.,* Bergamaschi *et al.* 1992; Lash *et al.* 2002; IARC 2012).

120. With respect to lifestyle factors[47] that could affect susceptibility of an individual to cancer, the effect of alcohol intake on trichloroethylene cancer hazard has been discussed

[47] Although I am not performing a causation assessment in this case, with respect to bladder cancer itself, lifestyle factors such as smoking must be considered as part of any specific causation assessment for an individual.

(*e.g.,* Koppel *et al.* 1988; Pastino *et al.* 2000; IARC 2012). Intake of alcohol is a common lifestyle factor to consider when liver enzymes are important to generation of reactive metabolites. With respect to all four of the chemicals at issue in this case, where CYP2E1 is involved in generation of reactive/toxic metabolites, alcohol consumption is known to induce the activity of the enzyme (*e.g.,* Oneta *et al.* 2002; Liangpunsakul *et al.* 2005; Jin *et al.* 2013); the result would be increased generation of the toxic metabolites.

121. All of the information related to inter-individual differences and susceptibility factors in the human population is important when considering how to assess specific causation of disease for any individual exposed to chemicals in the water at Camp Lejeune. Given the documented effects of inter-individual differences and susceptibility factors on the toxicity response to these four chemicals (perchloroethylene, trichloroethylene, benzene, and vinyl chloride), the most scientifically reliable method for specific causation would not be a risk calculation exercise, but instead would be a differential diagnosis process. This is because as part of differential diagnosis, factors that could affect the hazard posed by exposure to the four chemicals that contaminated the water at Camp Lejeune would be accounted for by a physician as part of a medical assessment of alternative causes for disease in that individual. A specific or individual risk calculation would not be able to account for the myriad of individual factors that could affect the exposure-response relationship in any human. Risk calculations are a useful tool for estimating risks *posed generally to a population* that has certain characteristics in terms of exposure (*i.e.,* routes of exposure possible; extent of exposures possible; duration of exposures possible).

IX. Conclusions

122. Based upon my education, training and experience, and considering the data and information identified and reviewed, I have formed opinions it this case that are based on a reasonable degree of scientific certainty. These opinions are:

- It is at least as likely as not that exposure to the mixture of chemicals that contaminated water at Camp Lejeune was hazardous to human health generally and posed a cancer hazard to humans.

- It is at least as likely as not that exposure to the Camp Lejeune water contaminated with perchloroethylene specifically is hazardous to human health, and that the human health hazard would include the development of bladder cancer.
- It is at least as likely as not that exposure to the Camp Lejeune water contaminated with trichloroethylene specifically is hazardous to human health, and that the human health hazard would include the development of bladder cancer.
- It is at least as likely as not that exposure to the Camp Lejeune water contaminated with benzene specifically is hazardous to human health, and that the human health hazard could include the development of bladder cancer.
- It is at least as likely as not that exposure to the Camp Lejeune water contaminated with vinyl chloride specifically is hazardous to human health, and that the human health hazard would include the development of cancer.
- Considered together, the scientific data and information related to the chemicals that contaminated the water at Camp Lejeune support at least four of the Hill considerations that are used as part of a general causation analysis. These Hill considerations include biologic plausibility, experiment, analogy, and coherence. Fulfillment of these four Hill considerations is supportive of a cause-and-effect relationship between exposure to the contaminated water and cancer, and specifically bladder cancer, in humans.
- When considered together, the scientific literature on the biological effects of trichloroethylene, perchloroethylene, and benzene provide sufficient evidence to show that exposure to these chemicals affect cellular mechanisms that have been linked to carcinogenesis and that a plausible biological mechanism for carcinogenesis following exposure to perchloroethylene, trichloroethylene, and benzene likely involves the steps of (1) formation of reactive metabolites in the liver and/or kidneys; (2) excretion of the reactive metabolites into urine where they come in contact with the cells that line the tissues of the urinary system that include the kidney, the renal pelvis, the ureters, and the bladder; and (3) interaction of the reactive and genotoxic metabolites of perchloroethylene, trichloroethylene, and benzene with urothelial cells that line the urinary tract from the renal pelvis to the ureter in humans to initiate carcinogenesis.
- When considered together with general principles of toxicology, the available data relating to the human health hazard of bladder cancer also must be considered in light of

the fact that human exposures at Camp Lejeune were to four different chemicals that each are associated with cancer hazard. As a result, in order to estimate risks posed to the populations of people that lived and worked at Camp Lejeune and were exposed to the contaminated water, a mixtures cancer risk assessment should be performed. When I performed such a population cancer risk assessment and only considered one relevant pathway of exposure, oral ingestion of water, the cancer risk assessment showed that people that lived or worked at Camp Lejeune were at an increased risk of developing cancer due to their exposure to the mixture of toxic chemicals that contaminated the water at Camp Lejeune.

- Given the documented effects of inter-individual differences and susceptibility factors on the toxicity response to the four chemicals that contaminated the water at Camp Lejeune, the most scientifically reliable method for specific causation would not be a risk calculation exercise, but instead would be a differential diagnosis process.

123. I hereby certify that this report is a complete and accurate statement of all my opinions, and the basis and reasons for them, to which I will testify under oath.

IX. Compensation

124. BioPolicy Solutions LLC is compensated at the rate of $400 per hour for my time on this matter. My compensation and that of BioPolicy Solutions is not determined by the outcome of this case.

References Cited

Abdelmegeend, MA *et al*. 2017. Cytochrome P450-2E1 is involved in aging-related kidney damage in mice through increased nitroxidative stress. *Food Chem Toxicol. Nov;109(Pt 1):48-59. doi: 10.1016/j.fct.2017.08.022*. Epub 2017 Aug 24. [Author Manuscript]

Agency for Toxic Substances and Disease Registry (ATSDR). 2024a.Toxicological Profile for Benzene Draft for Public Comment. October 2024. Department of Health and Human Services. *https://www.atsdr.cdc.gov/ToxProfiles/tp3.pdf*

Agency for Toxic Substances and Disease Registry (ATSDR). 2024b.Toxicological Profile for Vinyl Chloride. January 2024. Department of Health and Human Services. *https://www.atsdr.cdc.gov/ToxProfiles/tp20.pdf*

Agency for Toxic Substances and Disease Registry (ATSDR). 2019a. Toxicological Profile for Tetrachloroethylene. June 2019. *https://www.atsdr.cdc.gov/ToxProfiles/tp18.pdf*

Agency for Toxic Substances and Disease Registry (ATSDR). 2019b. Toxicological Profile for Trichloroethylene. June 2019. *https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf*

Agency for Toxic Substances and Disease Registry (ATSDR). 2017a. ATSDR Public health assessment for Camp Lejeune drinking water. U.S. Marine Corps base Camp Lejeune, North Carolina. January 20, 2017. U.S. Department of Health and Human Services, Agency for Toxic Subsances and Disease Registry.

Agency for Toxic Substances and Disease Registry (ATSDR). 2017b. ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases. January 13, 2017. U.S. Department of Health and Human Services. *https://www.atsdr.cdc.gov/camp-lejeune/data-research/index.html*

Anderson, D *et al.* 1995. An investigation of the DNA-damaging ability of benzene and its metabolites in human lymphocytes, using the comet assay. *Environ Mol Mutagen. 26(4):305-14. doi: 10.1002/em.2850260406.*

Anna, CH *et al.* 1994. ras proto-oncogene activation in dichloroacetic acid-, trichloroethylene- and tetrachloroethylene-induced liver tumors in B6C3F1 mice. *Carcinogenesis. Oct;15(10):2255-61. doi: 10.1093/carcin/15.10.2255.*

Aschengrau, A *et al.* 1993. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. *Arch Environ Health. Sep-Oct;48(5):284-92. doi: 10.1080/00039896.1993.9936715.*

Astrand, I and P Ovrum. 1976. Exposure to trichloroethylene I. Uptake and distribution in man. *Scand J Work Environ Health. Dec;2(4):199-211*.

Barale, R *et al*. 1990. Genotoxicity of two metabolites of benzene: phenol and hydroquinone show

strong synergistic effects in vivo. *Mutat Res. May;244(1):15-20. doi: 10.1016/0165-7992(90)90101-o*.

Barreto, G *et al* 2009. The role of catechols and free radicals in benzene toxicity: an oxidative DNA damage pathway. *Environ Mol Mutagen. Dec;50(9):771-80. doi: 10.1002/em.20500.*

Bartonicek, V. 1962. Metabolism and excretion of trichloroethylene after inhalation by human subjects. *Br J Ind Med. Apr;19(2):134-41. doi: 10.1136/oem.19.2.134.*

Bergamaschi, E *et al.* 1992. Rat model of perchloroethylene-induced renal dysfunctions. *Environ Res. Dec;59(2):427-39. doi: 10.1016/s0013-9351(05)80046-5.*

Blair, A *et al.* 2003. Extended mortality follow-up of a cohort of dry cleaners. *Ann Epidemiol. Jan;13(1):50-6. doi: 10.1016/s1047-2797(02)00250-8.*

Boice, JD, Jr. *et al*. 1999. Mortality among aircraft manufacturing workers. *Occup Environ Med. Sep;56(9):581-97. doi: 10.1136/oem.56.9.581.*

Bolt, HM. 2005. Vinyl chloride-a classical industrial toxicant of new interest. *Crit Rev Toxicol. Apr-May;35(4):307-23. doi: 10.1080/10408440490915975.*

Bolt, HM *et al.* 1977. Pharmacokinetics of vinyl chloride in the rat. *Toxicology. Apr;7(2):179-88. doi: 10.1016/0300-483x(77)90063-4.*

Bolt, HM *et al.* 1976. Disposition of (1,2-14C) vinyl chloride in the rat. *Arch Toxicol. Jun 8;35(3):153-62. doi: 10.1007/BF00293562.*

Boorman, GA *et al*. 1994. Rodent carcinogenicity bioassay: past, present, and future. *Toxicol Pathol. Mar-Apr;22(2):105-11. doi: 10.1177/019262339402200204.*

Bove, FJ *et al*. 2024a. 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. Jul 3;23(1):61. doi: 10.1186/s12940-024-01099-7.*

Bove, FJ *et al*. 2024b. 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. Oct;132(10):107008. doi: 10.1289/EHP14966.* Epub 2024 Oct 24.

Bove, FJ *et al*. 2014a. Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. *Environ Health. Feb 19;13(1):10. doi: 10.1186/1476-069X-13-10.*

Bove, FJ *et al*. 2014b. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environ Health. Aug 13;13:68. doi: 10.1186/1476-069X-13-68.*

Brüning, T *et al*. 1998. Acute intoxication with trichloroethene: clinical symptoms, toxicokinetics, metabolism, and development of biochemical parameters for renal damage. *Toxicol Sci. Feb;41(2):157-65. doi: 10.1006/toxs.1997.2401.*

Buchter, A *et al*. 1977. [Distribution of vinyl chloride in rats (author's transl)]. *Int Arch Occup Environ Health. Apr 15;39(1):27-32. doi: 10.1007/BF00381548.*

Bull, RJ *et al*. 2002. Contribution of dichloroacetate and trichloroacetate to liver tumor induction in mice by trichloroethylene. *Toxicol Appl Pharmacol. Jul 1;182(1):55-65. doi: 10.1006/taap.2002.9427.*

Burns, PB and GM Swanson. 1991. Risk of urinary bladder cancer among blacks and whites: the role of cigarette use and occupation. *Cancer Causes Control. Nov;2(6):371-9. doi: 10.1007/BF00054297.*

Calvert GM *et al.* 2011. Mortality and end-stage renal disease incidence among dry cleaning workers. *Occup Environ Med. Oct;68(10):709-16. doi: 10.1136/oem.2010.060665.* Epub 2010 Dec 16.

Castorina, R and TJ Woodruff. 2003. Assessment of potential risk levels associated with U.S. Environmental Protection Agency reference values. *Environ Health Perspect. Aug;111(10):1318-25. doi: 10.1289/ehp.6185.*

Ceballos, DM *et al* 2021. Perchloroethylene and dry cleaning: It's time to move the industry to safer alternatives. *Front Public Health. Mar 5;9:638082. doi: 10.3389/fpubh.2021.638082. eCollection 2021.*

Chen, MJ *et al.* 2003. A new approach to estimating the volatilization rates of shower water-contained volatile organic compounds during showering. *Atmospheric Environment, 37(31):4325-4333.*

Chiang, SY *et al.* 1997. Mutagenicity of vinyl chloride and its reactive metabolites, chloroethylene oxide and chloroacetaldehyde, in a metabolically competent human B-lymphoblastoid line. *Carcinogenesis. Jan;18(1):31-6. doi: 10.1093/carcin/18.1.31.*

Chiu, WA *et al.* 2013. Human health effects of trichloroethylene: key findings and scientific issues. *Environ Health Perspect. Mar;121(3):303-11. doi: 10.1289/ehp.1205879.* Epub 2012 Dec 18.

Christensen, KY *et al*. 2013. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal. *J Occup Environ Med. Feb;55(2):198-208. doi: 10.1097/JOM.0b013e3182728eab.*

Cichocki, JA *et al*. 2016. Target Organ Metabolism, Toxicity, and Mechanisms of Trichloroethylene and Perchloroethylene: Key Similarities, Differences, and Data Gaps. *J Pharmacol Exp Ther. Oct;359(1):110-23. doi: 10.1124/jpet.116.232629.* Epub 2016 Aug 10.

Clay, P. 2008. Assessment of the genotoxicity of trichloroethylene and its metabolite, S-(1,2-dichlorovinyl)-L-cysteine (DCVC), in the comet assay in rat kidney. *Mutagenesis. Jan;23(1):27-*

33. doi: 10.1093/mutage/gem034. Epub 2007 Nov 13.

Colt, JS *et al*. 2011. Occupation and bladder cancer in a population-based case-control study in Northern New England. *Occup Environ Med. Apr;68(4):239-49. doi: 10.1136/oem.2009.052571.* Epub 2010 Sep 23.

Cordier, S *et al.* 1993. Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol. Jun;22(3):403-11. doi: 10.1093/ije/22.3.403.*

Cronkite, EP *et al.* 1989. Hematotoxicity and carcinogenicity of inhaled benzene. *Environ Health Perspect. Jul;82:97-108. doi: 10.1289/ehp.898297.*

D'Souza, RW *et al.* 1985. Oral and intravenous trichloroethylene pharmacokinetics in the rat. *J Toxicol Environ Health. 15(5):587-601. doi: 10.1080/15287398509530688.*

Dallas, CE *et al.* 1995. Physiologically based pharmacokinetic model useful in prediction of the influence of species, dose, and exposure route on perchloroethylene pharmacokinetics. *J Toxicol Environ Health. Mar;44(3):301-17. doi: 10.1080/15287399509531961.*

Dallas, CE *et al.* 1994a. Use of tissue disposition data from rats and dogs to determine species differences in input parameters for a physiological model for perchloroethylene. *Environ Res. Oct;67(1):54-67. doi: 10.1006/enrs.1994.1064.*

Dallas, CE *et al.* 1994b. Development of a physiologically based pharmacokinetic model for perchloroethylene using tissue concentration-time data. *Toxicol Appl Pharmacol. Sep;128(1):50-9. doi: 10.1006/taap.1994.1179.*

Dallas, CE *et al*. 1991. Physiological pharmacokinetic modeling of inhaled trichloroethylene in rats. *Toxicol Appl Pharmacol. Sep 1;110(2):303-14. doi: 10.1016/s0041-008x(05)80013-4.*

Dekant, W *et al.* 1986a. Bacterial beta-lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. *Chem Biol Interact. Oct 15;60(1):31-45. doi: 10.1016/0009-2797(86)90015-3.*

Dekant, W *et al.* 1986b. Absorption, elimination and metabolism of trichloroethylene: a quantitative comparison between rats and mice. *Xenobiotica. Feb;16(2):143-52. doi: 10.3109/00498258609043517.*

DeMarini, DM *et al.* 1994. Dichloroacetic acid and related compounds: induction of prophage in E. coli and mutagenicity and mutation spectra in Salmonella TA100. *Mutagenesis. Sep;9(5):429-37. doi: 10.1093/mutage/9.5.429.*

Dreessen, B *et al.* 2003. Mutagenicity of the glutathione and cysteine S-conjugates of the haloalkenes 1,1,2-trichloro-3,3,3-trifluoro-1-propene and trichlorofluoroethene in the Ames test in comparison with the tetrachloroethene-analogues. *Mutat Res. Aug 5;539(1-2):157-66. doi: 10.1016/s1383-5718(03)00160-8.*

Dzubow, RB *et al.* 2010. Early lifestage exposure and potential developmental susceptibility to tetrachloroethylene. *Birth Defects Res B Dev Reprod Toxicol. Feb;89(1):50-65. doi: 10.1002/bdrb.20222.*

Elfarra, AA and RJ Krause. 2007. S-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide, a reactive metabolite of S-(1,2,2-Trichlorovinyl)-L-cysteine formed in rat liver and kidney microsomes, is a potent nephrotoxicant**.** *J Pharmacol Exp Ther. Jun;321(3):1095-101. doi: 10.1124/jpet.107.120444.* Epub 2007 Mar 8.

EPA. 2022. Final revised unreasonable risk determination for perchloroethylene. Assessing and managing chemicals under TSCA. U.S. Environmental Agency. Washington, DC. December 2022. https://www.epa.gov/system/files/documents/2022-12/PCE_Final%20Revised%20RD_12-5-22.pdf

EPA. 2020a. Risk evaluation for perchloroethylene (ethene, 1,1,2,2-tetrachloro-) CASRN: 127-18-4. Office of Chemical Safety and Pollution Prevention. U.S. Environmental Protection Agency. EPA Document #740-R1-8011. December 2020. https://www.epa.gov/sites/default/files/2020-12/documents/1_risk_evaluation_for_perchloroethylene_pce_casrn_127-18-4_0.pdf

EPA 2020b. Risk evaluation for trichloroethylene. CASRN: 79-01-6. Office of Chemical Safety and Pollution Prevention. U.S. Environmental Protection Agency. EPA Document #740R18008. November 2020. https://www.epa.gov/sites/default/files/2020-11/documents/1._risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf

EPA. 2012. Toxicological review of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4). In support of summary information on the Integrated Risk Information System (IRIS). February 2012. U.S. Environmental Protection Agency. Washington, DC. EPA/635/R-08/011F. https://iris.epa.gov/static/pdfs/0106tr.pdf.

EPA. 2011. Toxicological review of trichloroethylene (CAS No. 79-01-6). In support of summary information on the Integrated Risk Information System (IRIS). September 2011. U.S. Environmental Protection Agency. Washington, DC. EPA/635/R-09/011F. https://iris.epa.gov/static/pdfs/Intro_0199tr.pdf

EPA. 2004. Risk assessment guidance for superfund Volume I: Human health evaluation manual (Part E, supplemental guidance for dermal risk assessment). Final. July 2004. USEPA/540/R/99/005. https://www.epa.gov/sites/default/files/2015-09/documents/part_e_final_revision_10-03-07.pdf

EPA 2000a. Toxicological review of vinyl chloride (CAS No. 75-01-4) in support of summary information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency. Washington, DC. May 2000. EPA/635R-00/004. https://iris.epa.gov/static/pdfs/1001tr.pdf

EPA 2000b.Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum. U.S. Environmental Protection Agency. Washington, DC. August 2000. https://assessments.epa.gov/risk/document/&deid=20533

EPA. 1998. Carcinogenic effects of benzene: an update. (Draft Report). National Center for

Environmental Assessment - Washington Office. Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/600/P-97/001F. April 1998. https://assessments.epa.gov/risk/document/&deid=2806#downloads

EPA. 1989. Risk assessment guidance for superfund Volume I: Human health evaluation manual (Part A). Interim Final. Office of Emergency and Remedial Response, U.S. Environmental Protection Agency, Washington, DC. EPA/540/1-89/002. https://www.epa.gov/sites/default/files/2015-09/documents/rags_a.pdf

EPA 1986a. Health effects assessment for vinyl chloride. Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-540/1-86-036. https://nepis.epa.gov/Exe/tiff2png.cgi/2000FDUW.PNG?-r+75+-g+7+D%3A%5CZYFILES%5CINDEX%20DATA%5C86THRU90%5CTIFF%5C00000794%5C2000FDUW.TIF

EPA 1986b. Guidelines for the health risk assessment of chemical mixtures. Risk Assessment Forum, U.S. Environmental Protection Agency. Washington, DC. EPA/630/R-98/002. September 1986. https://www.epa.gov/sites/default/files/2014-11/documents/chem_mix_1986.pdf.

Erexson, GL *et al.* 1985. Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites in vitro. *Cancer Res. Jun;45(6):2471-7.*

Farris, GM *et al.* 1993. Carcinogenicity of inhaled benzene in CBA mice. *Fundam Appl Toxicol. May;20(4):503-7. doi: 10.1006/faat.1993.1061.*

Faustman, EM. 2019. Risk Assessment. In: *Casarett and Doull's Toxicology, The Basic Science of Poisons. 9th*. Curtis D.Klaassen, Ph.D. (ed) The McGraw-Hill Companies, Inc. New York, NY. Chapter 4, pp: 127-155.

Feingold, A and DA Holaday. 1977. The pharmacokinetics of metabolism of inhalation anaesthetics. A simulation study. *Br J Anaesth. Feb;49(2):155-62. doi: 10.1093/bja/49.2.155.*

Fernández, JG *et al.* 1977. Trichloroethylene exposure. Simulation of uptake, excretion, and metabolism using a mathematical model. *Br J Ind Med. Feb;34(1):43-55. doi: 10.1136/oem.34.1.43.*

Feron, VJ *et al.* 1981. Lifespan oral toxicity study of vinyl chloride in rats. *Food Cosmet Toxicol. Jun;19(3):317-33. doi: 10.1016/0015-6264(81)90391-6.*

Filser, JG and HM Bolt. 1979. Pharmacokinetics of halogenated ethylenes in rats. *Arch Toxicol. Jun 8;42(2):123-36. doi: 10.1007/BF00316492.*

Frantz, SW and PG Watanabe. 1983. Tetrachloroethylene: balance and tissue distribution in male Sprague-Dawley rats by drinking-water administration. *Toxicol Appl Pharmacol. Jun 15;69(1):66-72. doi: 10.1016/0041-008x(83)90120-5.*

Fukuda, K *et al*. 1983. Inhalation carcinogenicity of trichloroethylene in mice and rats. *Ind Health. 21(4):243-54. doi: 10.2486/indhealth.21.243.*

Gaertner, RR *et al.* 2004. A case-control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control. Dec;15(10):1007-19. doi: 10.1007/s10552-004-1448-7.*

Gehring, PJ *et al.* 1978. Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example--vinyl chloride. *Toxicol Appl Pharmacol. Jun;44(3):581-91. doi: 10.1016/0041-008x(78)90266-1.*

Ghantous, H and BR Danielsson. 1986. Placental transfer and distribution of toluene, xylene and benzene, and their metabolites during gestation in mice. *Biol Res Pregnancy Perinatol. 7(3):98-105.*

Goldstein, BD *et al.* 1982. Myelogenous leukemia in rodents inhaling benzene. *Toxicol Lett. Oct;13(3-4):169-73. doi: 10.1016/0378-4274(82)90206-5.*

Gut, I *et al.* 1996. Cytochromes P450 in benzene metabolism and involvement of their metabolites and reactive oxygen species in toxicity. *Environ Health Perspect. Dec;104 Suppl 6(Suppl 6):1211-8. doi: 10.1289/ehp.961041211.*

Hadkhale, K *et al* 2017. Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries. *Int J Cancer. Apr 15;140(8):1736-1746. doi: 10.1002/ijc.30593.* Epub 2017 Jan 19.

Halaseh, SA *et al.* 2022. A review of the etiology and epidemiology of bladder cancer: All you need to know. *Cureus. Jul 27;14(7):e27330. doi: 10.7759/cureus.27330. eCollection 2022 Jul.*

Hansen, J *et al*. 2013. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. *J Natl Cancer Inst. Jun 19;105(12):869-77. doi: 10.1093/jnci/djt107.* Epub 2013 May 30.

Heatlh Canada. 2013. Guidelines for Canadian drinking water quality. Guideline technical document. Vinyl chloride. *Prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.* Ottawa, Ontario. March 2013. https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-vinyl-chloride-chlorure-vinyle-eau/alt/water-vinyl-chloride-chlorure-vinyle-eau-eng.pdf

Health Canada. 2005. Guidelines for Canadian drinking water quality: Supporting documentation - Trichloroethylene. *Prepared for the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment*. Ottawa, Ontario. May 2005. https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-trichloroethylene-eau/alt/water-trichloroethylene-eau-eng.pdf

Henderson, RF *et al.* 1989. The effect of dose, dose rate, route of administration, and species on tissue and blood levels of benzene metabolites. *Environ Health Perspect. Jul;82:9-17. doi: 10.1289/ehp.89829.*

Herren-Freund, SL *et al.* 1987. The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. *Toxicol Appl Pharmacol. Sep 15;90(2):183-9. doi: 10.1016/0041-008x(87)90325-5.*

Hildesheim, A *et al.* 1997. CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst. Aug 20;89(16):1207-12. doi: 10.1093/jnci/89.16.1207.*

Hill, AB. 1965. The environment and disease: Association or causation? *Proc. R. Soc. Med. 58:295-300.*

Hsieh, HI *et al.* 2007. Effect of the CYP2E1 genotype on vinyl chloride monomer-induced liver fibrosis among polyvinyl chloride workers. T*oxicology. Sep 24;239(1-2):34-44. doi: 10.1016/j.tox.2007.06.089.* Epub 2007 Jun 27.

Hu, Y *et al*. 1997. Genetic polymorphism of human CYP2E1: characterization of two variant alleles. *Mol Pharmacol. Mar;51(3):370-6.*

Huff, J. 2007. Benzene-induced cancers: abridged history and occupational health impact. *Int J Occup Environ Health. Apr-Jun;13(2):213-21. doi: 10.1179/oeh.2007.13.2.213.*[Author Manuscript]

International Agency for Research on Cancer (IARC). 2018. Benzene. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 120*. 2018. ISBN: 978-92-832-0187-8. https://publications.iarc.fr/576

International Agency for Research on Cancer (IARC). 2012. Some chemicals present in industrial and consumer products, food and drinking water. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 101.* February 2011. ISBN-13: 978-92-832-1324-6; 978-92-832-0139-7. https://publications.iarc.fr/125

International Agency for Research on Cancer (IARC). 2008. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 97*. 2008. ISBN-13: 978-92-832-1297-3; 978-92-832-1597-4. https://publications.iarc.fr/115

International Agency for Research on Cancer (IARC). 1997. Polychlorinated Dibenzo- para-dioxins and Polychlorinated Dibenzofurans, IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 69*. October 1979. ISBN-13: 978-92-832-1269-0; 978-92-832-1569-1. February 1997. https://publications.iarc.fr/87

International Agency for Research on Cancer (IARC). 1995. Dry cleaning, some chlorinated solvents and other industrial chemicals. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 63*. February 1995. ISBN-13: 978-92-832-1263-8. https://publications.iarc.fr/81

International Agency for Research on Cancer (IARC). 1987. IARC. Overall evaluations of

carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monographs Supplement 7*. ISBN-13: 978-92-832-1411-3. https://publications.iarc.fr/139

International Agency for Research on Cancer (IARC). 1979. Some halogenated hydrocarbons. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 20*. October 1979. ISBN-13: 978-92-832-1220-1. https://publications.iarc.fr/38

Ijaz, M *et al.* 2024. Genetic polymorphisms in FABP2, CYP2E1, and TP53 genes are potentially associated with colorectal cancer susceptibility. *Sci Rep. Sep 3;14(1):20464. doi: 10.1038/s41598-024-70381-y.*

Ikeda, M. 1977. Metabolism of trichloroethylene and tetrachloroethylene in human subjects. *Environ Health Perspect. Dec;21:239-45. doi: 10.1289/ehp.7721239.*

Irving, RM and AA Elfarra. 2013. Mutagenicity of the cysteine S-conjugate sulfoxides of trichloroethylene and tetrachloroethylene in the Ames test. *Toxicology. Apr 5;306:157-61. doi: 10.1016/j.tox.2013.02.003*. Epub 2013 Feb 13.

Ivanetich, KM *et al.* 1977. The interaction of vinyl chloride with rat hepatic microsomal cytochrome P-450 in vitro. *Biochem Biophys Res Commun. Feb 21;74(4):1411-8. doi: 10.1016/0006-291x(77)90599-x.*

Jaffe, DR *et al.* 1985. Production of DNA single strand breaks in rabbit renal tissue after exposure to 1,2-dichlorovinylcysteine. *Toxicology. Apr;35(1):25-33. doi: 10.1016/0300-483x(85)90129-5.*

Jin, M *et al.* 2013. Regulation of cytochrome P450 2e1 expression by ethanol: role of oxidative stress-mediated pkc/jnk/sp1 pathway. *Cell Death Dis. Mar 21;4(3):e554. doi: 10.1038/cddis.2013.78.*

JISA. 1993. Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice. Japan Industrial Safety Association, Hadano, Japan. (ABSTRACT ONLY). https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/630653

Kawasaki, Y *et al.* 2009. Benzene-induced hematopoietic neoplasms including myeloid leukemia in Trp53-deficient C57BL/6 and C3H/He mice. *Toxicol Sci. Aug;110(2):293-306. doi: 10.1093/toxsci/kfp107.* Epub 2009 May 28.

Kielhorn, J *et al.* 2000. Vinyl chloride: still a cause for concern. *Environ Health Perspect. Jul;108(7):579-88. doi: 10.1289/ehp.00108579.*

Klaunig, JE and Z Wang. 2019. Chemical Carcinogenesis. In: Casarett and Doull's Toxicology, The Basic Science of Poision. 9th Edition. CD Klassen, Ph.D (ed.), The McGraw-Hill Companies, Inc. New York, NY. Chapter 9.

Knutsen, JS *et al.* 2013a. A calibrated human PBPK model for benzene inhalation with urinary bladder and bone marrow compartments. *Risk Anal. Jul;33(7):1237-51. doi: 10.1111/j.1539-6924.2012.01927.x.* Epub 2012 Dec 24.

Knutsen, JS *et al.* 2013b. Supplemental Material: A calibrated human PBPK model for benzene inhalation with urinary bladder and bone marrow compartments. *Risk Anal. Jul;33(7):1237-51. doi: 10.1111/j.1539-6924.2012.01927.x.* Epub 2012 Dec 24.

Köppel, C *et al.* 1988. Acute trichloroethylene poisoning with additional ingestion of ethanol--concentrations of trichloroethylene and its metabolites during hyperventilation therapy. *Intensive Care Med. 14(1):74-6. doi: 10.1007/BF00254128.*

Krajewski, J *et al.* 1980. Retention of vinyl chloride in the human lung. *Br J Ind Med. Nov;37(4):373-4. doi: 10.1136/oem.37.4.373.*

Krewski, D *et al.* 1991. A model-free approach to low-dose extrapolation*. Environ Health Perspect. Jan;90:279-85. doi: 10.1289/ehp.90-1519485.*

Laham, S. 1970. Studies on placental transfer. Trichlorethylene. *IMS Ind Med Surg. Jan;39(1):46-9.*

Laitinen, J *et al.* 1994. Short time exposure to benzene and gasoline at garages. *Chemosphere, 28(1):197-205. https://doi.org/10.1016/0045-6535(94)90213-5*

Lash, LH. 2024. Trichloroethylene: An Update on an Environmental Contaminant with Multiple Health Effects. *Annu Rev Pharmacol Toxicol. Aug 2. doi: 10.1146/annurev-pharmtox-022724-120525.*

Lash, LH and JC Parker. 2001. Hepatic and renal toxicities associated with perchloroethylene. *Pharmacol Rev. Jun;53(2):177-208.*

Lash, LH *et al.* 2014. Trichloroethylene biotransformation and its role in mutagenicity, carcinogenicity and target organ toxicity. *Mutat Res Rev Mutat Res. Oct-Dec;762:22-36. doi: 10.1016/j.mrrev.2014.04.003.*

Lash, LH *et al*. 2007. Modulation of hepatic and renal metabolism and toxicity of trichloroethylene and perchloroethylene by alterations in status of cytochrome P450 and glutathione. *Toxicology. Jun 3;235(1-2):11-26. doi: 10.1016/j.tox.2007.03.001*. Epub 2007 Mar 12.

Lash, LH *et al.* 2003. Roles of necrosis, Apoptosis, and mitochondrial dysfunction in S-(1,2-dichlorovinyl)-L-cysteine sulfoxide-induced cytotoxicity in primary cultures of human renal proximal tubular cells. *J Pharmacol Exp Ther. Jun;305(3):1163-72. doi: 10.1124/jpet.102.046185*. Epub 2003 Mar 6.

Lash, LH *et al.* 2002. Renal toxicity of perchloroethylene and S-(1,2,2-trichlorovinyl)glutathione in rats and mice: sex- and species-dependent differences. *Toxicol Appl Pharmacol. Mar 15;179(3):163-71. doi: 10.1006/taap.2001.9358.*

Lash, LH *et al*. 2001. Apoptosis, necrosis, and cell proliferation induced by S-(1,2-dichlorovinyl)-L-cysteine in primary cultures of human proximal tubular cells. *Toxicol Appl Pharmacol. Nov 15;177(1):1-16. doi: 10.1006/taap.2001.9295.*

Lash, LH *et al.* 2000b. Metabolism of trichloroethylene. *Environ Health Perspect. May;108 Suppl*

2(Suppl 2):177-200. doi: 10.1289/ehp.00108s2177.

Lee, KM *et al.* 2000a. Contribution of direct solvent injury to the dose-dependent kinetics of trichloroethylene: portal vein administration to rats. *Toxicol Appl Pharmacol. Apr 1;164(1):46-54. doi: 10.1006/taap.2000.8891.*

Lee, KM *et al.* 2000b. Mechanisms of the dose-dependent kinetics of trichloroethylene: oral bolus dosing of rats. *Toxicol Appl Pharmacol. Apr 1;164(1):55-64. doi: 10.1006/taap.2000.8892.*

Li, GX *et al.* 2006. Thioredoxin overexpression in mice, model of attenuation of oxidative stress, prevents benzene-induced hemato-lymphoid toxicity and thymic lymphoma. *Exp Hematol. Dec;34(12):1687-97. doi: 10.1016/j.exphem.2006.08.005.*

Liangpunsakul, S *et al*. 2005. Activity of CYP2E1 and CYP3A enzymes in adults with moderate alcohol consumption: a comparison with nonalcoholics. *Hepatology. May;41(5):1144-50. doi: 10.1002/hep.20673.*

Lindstrom, AB *et al.* 1997. Measurement of benzene oxide in the blood of rats following administration of benzene. *Carcinogenesis. Aug;18(8):1637-41. doi: 10.1093/carcin/18.8.1637.*

Lindstrom, AB *et al*. 1994. Gasoline-contaminated ground water as a source of residential benzene exposure: a case study. *J Expo Anal Environ Epidemiol. Apr-Jun;4(2):183-95.*

Liu, H and R Baliga. 2003. Cytochrome P450 2E1 null mice provide novel protection against cisplatin-induced nephrotoxicity and apoptosis. *Kidney Int. May;63(5):1687-96. doi: 10.1046/j.1523-1755.2003.00908.x.*

Luo, L *et al.* 2008. Hydroquinone-induced genotoxicity and oxidative DNA damage in HepG2 cells. *Chem Biol Interact. May 9;173(1):1-8. doi: 10.1016/j.cbi.2008.02.002.* Epub 2008 Feb 14.

Luo, YS *et al.* 2018. Metabolism and toxicity of trichloroethylene and tetrachloroethylene in cytochrome P450 2E1 knockout and humanized transgenic mice. *Toxicol Sci. Aug 1;164(2):489-500. doi: 10.1093/toxsci/kfy099.*

Lynge, E *et al.* 2006. Cancer in persons working in dry cleaning in the Nordic countries. *Environ Health Perspect. Feb;114(2):213-9. doi: 10.1289/ehp.8425.*

Mallin, K. 1990. Investigation of a bladder cancer cluster in northwestern Illinois. *Am J Epidemiol. 1990 Jul;132(1 Suppl):S96-106. doi: 10.1093/oxfordjournals.aje.a115795.*

Mally, A *et al.* 2006. Analysis of renal cell transformation following exposure to trichloroethene in vivo and its metabolite S-(dichlorovinyl)-L-cysteine in vitro. *Toxicology. Jul 5;224(1-2):108-18. doi: 10.1016/j.tox.2006.04.036.* Epub 2006 Apr 28.

Maltoni, C *et al.* 1989. Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. *Environ Health Perspect. Jul;82:109-24. doi: 10.1289/ehp.8982109.*

Maltoni, C *et al.* 1988a. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. *Ann N Y Acad Sci. 534:316-42. doi: 10.1111/j.1749-6632.1988.tb30120.x.*

Maltoni, C *et al.* 1988b. Further evidence of benzene carcinogenicity. Results on Wistar rats and Swiss mice treated by ingestion. *Ann N Y Acad Sci. 534:412-26. doi: 10.1111/j.1749-6632.1988.tb30131.x.*

Maltoni, C *et al.* 1986. Experimental research on trichloroethylene carcinogenesis. In: *Archives of research on industrial carcinogenesis; v. 5*. ISBN/ISSN: 9780911131406; 091113140X

Maltoni, C *et al.* 1985. Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: current results and ongoing research. *Am J Ind Med. 7(5-6):415-46. doi: 10.1002/ajim.4700070508.*

Maltoni, C *et al.* 1983. Benzene: a multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. *Am J Ind Med. 4(5):589-630. doi: 10.1002/ajim.4700040503.*

Maltoni, C *et al.* 1982. Squamous cell carcinomas of the oral cavity in Sprague-Dawley rats, following exposure to benzene by ingestion. First experimental demonstration. *Med Lav. Jul-Aug;73(4):441-5.*

Maltoni, C *et al.* 1981. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. *Environ Health Perspect. Oct;41:3-29. doi: 10.1289/ehp.81413.*

Maltoni, C and C Scarnato. 1979. First experimental demonstration of the carcinogenic effects of benzene; long-term bioassays on Sprague-Dawley rats by oral administration. *Med Lav. Sep-Oct;70(5):352-7.*

Miller, MF *et al*. 2017. Low-dose mixture hypothesis of carcinogenesis workshop: Scientific underpinnings and research recommendations. *Environ Health Perspect. Feb;125(2):163-169. doi: 10.1289/EHP411*. Epub 2016 Aug 12.

Modjtahedi, BS and HI Maibach. 2008. In vivo percutaneous absorption of benzene in man: forearm and palm. *Food Chem Toxicol. Mar;46(3):1171-4. doi: 10.1016/j.fct.2007.11.014.* Epub 2007 Nov 28.

Monster, A. *et al.* 1983. Biological monitoring of occupational exposure to tetrachloroethene. *Scand J Work Environ Health. Jun;9(3):273-81. doi: 10.5271/sjweh.2409.*

Monster, AC. 1986. Biological monitoring of chlorinated hydrocarbon solvents. *J Occup Med. Aug;28(8):583-8. doi: 10.1097/00043764-198608000-00012.*

Monster, AC. 1979. Difference in uptake, elimination, and metabolism in exposure to trichloroethylene,

1,1,1-trichloroethane and tetrachloroethylene. *Int Arch Occup Environ Health. 1979 Jan 15;42(3-4):311-7. doi: 10.1007/BF00377785.*

Monster, AC *et al.* 1979a Kinetics of tetrachloroethylene in volunteers; influence of exposure concentration and work load. *Int Arch Occup Environ Health. Jan 15;42(3-4):303-9. doi: 10.1007/BF00377784*

Monster, AC *et al*. 1979b. Kinetics of trichloroethylene in repeated exposure of volunteers. *Int Arch Occup Environ Health. Jan 15;42(3-4):283-92. doi: 10.1007/BF00377782.*

Monster, AC *et al.* 1976. Pharmacokinetics of trichloroethylene in volunteers, influence of workload and exposure concentration. *Int Arch Occup Environ Health. Dec 15;38(2):87-102. doi: 10.1007/BF00378619.*

Moore, LE *et al*. 2010. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. *Cancer Res. Aug 15;70(16):6527-36. doi: 10.1158/0008-5472.CAN-09-4167.* Epub 2010 Jul 27.

Morgan, RW *et al.* 1998. Mortality of aerospace workers exposed to trichloroethylene. *Epidemiology. Jul;9(4):424-31.*

Nadler, DL and IG Zurbenko. 2014. Estimating Cancer Latency Times Using a Weibull Model. *Advances in Epidemiology, 2014(1):746769.* https://onlinelibrary.wiley.com/doi/abs/10.1155/2014/746769

Nadler, DL and IG Zurbenko. 2013. Developing a Weibull model extension to estimate cancer latency. *International Scholarly Res. Notices. 2013(1):750857. https://doi.org/10.5402/2013/750857.*

Nakai, JS *et al.* 1999. Penetration of chloroform, trichloroethylene, and tetrachloroethylene through human skin. *J Toxicol Environ Health A. Oct 15;58(3):157-70. doi: 10.1080/009841099157368.*

National Cancer Institute (NCI). 1977. Bioassay of tetrachloroethylene for possible carcinogenicity. Bethesda, MD: National Cancer Institute. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publ (NIH) 77-813. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr013.pdf

National Cancer Institute (NCI). 1976. Carcinogenesis bioassay of trichloroethylene (CAS No. 79-01-6). Bethesda, MD: National Cancer Institute, Division of Cancer Cause and Prevention, Carcinogenesis Program, Carcinogen Bioassay and Program Resources Branch. NCI-CG-TR-2, DHEW Publ. No. (NIH) 76-802. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr002.pdf

Neafsey, P *et al.* 2009. Genetic polymorphism in CYP2E1: Population distribution of CYP2E1 activity. *J Toxicol Environ Health B Crit Rev. 12(5-6):362-88. doi: 10.1080/10937400903158359.*

Nebert, DW *et al.* 2002. NAD(P)H:quinone oxidoreductase (NQO1) polymorphism, exposure to benzene, and predisposition to disease: a HuGE review. *Genet Med. Mar-Apr;4(2):62-70. doi:*

10.1097/00125817-200203000-00003.

Nomiyama, K and H Nomiyama. 1974. Respiratory elimination of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed. 32(1):85-91. doi: 10.1007/BF00539098.*

National Research Council (NRC). 2011. Reference Manual on Scientific Evidence. Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence; Committee on Science, Technology, and Law Policy and Global Affairs. National Academy Press, Washington, D.C. 2011. https://doi.org/10.17226/776

National Research Council (NRC). 2010. Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene. Washington, DC: The National Academies Press. https://doi.org/10.17226/12863.

National Research Council (NRC). 2006. Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. Washington, DC: The National Academies Press. https://doi.org/10.17226/11707.

National Toxicology Program (NTP). 1988. Toxicology and carcinogenesis studies of of trichloroethylene (Cas No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies). April 1988. Report No. NTP TR 273. NIH Publication No. 88-2529. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

National Toxicology Program (NTP). 1986a. Toxicology and carcinogenesis tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F$_1$ mice (inhalation studies. August 1986. Report No. NTP TR 311. NIH Publication No. 86-2567. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

National Toxicology Program (NTP). 1986b. Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F$_1$ mice. April 1986.. April 1986. Report No. NTP TR 289. NIH Publication No. 86-2545. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

National Research Council (NRC). 1983. Risk Assessment in the Federal Government: Managing the Process. Committee on the Institutional Means for Assessment of Risks to Public Health. Commission on Life, Sciences. National Academy Press, Washington, D.C. 1983. https://doi.org/10.17226/776

National Toxicology Program (NTP). 2015. Monograph on Trichloroethylene. In: *Report on Carcinogens, Monograph 05, January 2015.* ISSN: 2331-267X. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

National Toxicology Program (NTP). 1990. Toxicology and carcinogenesis studies of of trichloroethylene (without epichlorohydrin) (Cas No. 79-01-6) in F344/N rats and B3C3F$_1$ Mice (Gavage Studies). May 1990. Report No. NTP TR 289. NIH Publication No. 90-1779. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

National Toxicology Program (NTP). 2021a. Tetrachloroethylene (CAS No. 127-18-4). In: *Report on Carcionogens (15th Edition).* U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.

National Toxicology Program (NTP). 2021b. Trichloroethylene (CAS No. 79-01-6). In: *Report on Carcionogens (15th Edition).* U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.

National Toxicology Program (NTP). 2021c. Benzene (CAS No. 71-43-2). In: *Report on Carcinogens (15th Edition).* U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.

National Toxicology Program (NTP). 2021d. Vinyl Chloride (CAS No. 75-01-4). In: *Report on Carcinogens (15th Edition).* U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.

Ohtsuki, T *et al.* 1983. Limited capacity of humans to metabolize tetrachloroethylene. *Int Arch Occup Environ Health. 51(4):381-90. doi: 10.1007/BF00378352.*

Oneta, CM *et al.* 2002. Dynamics of cytochrome P4502E1 activity in man: induction by ethanol and disappearance during withdrawal phase. *J Hepatol. Jan;36(1):47-52. doi: 10.1016/s0168-8278(01)00223-9.*

Opdam, JJ and JF Smolders. 1986. Alveolar sampling and fast kinetics of tetrachloroethene in man. I. Alveolar sampling. *Br J Ind Med. Dec;43(12):814-24. doi: 10.1136/oem.43.12.814.*

Parke, DV and RT Williams. 1953. Studies in detoxication. XLIX. The metabolism of benzene containing (14C1) benzene. *Biochem J. May;54(2):231-8. doi: 10.1042/bj0540231.*

Pastino, GM *et al.* 2000. Human variability and susceptibility to trichloroethylene. *Environ Health Perspect. May;108 Suppl 2(Suppl 2):201-14. doi: 10.1289/ehp.00108s2201.*

Pegg, DG *et al.* 1979. Disposition of tetrachloro(14C)ethylene following oral and inhalation exposure in rats. *Toxicol Appl Pharmacol. Dec;51(3):465-74. doi: 10.1016/0041-008x(79)90371-5.*

Pekari, K *et al.* 1992. Biological monitoring of occupational exposure to low levels of benzene. *Scand J Work Environ Health. Oct;18(5):317-22. doi: 10.5271/sjweh.1570.*

Peng, C *et al*. 2013. Genotoxicity of hydroquinone in A549 cells. *Cell Biol Toxicol. Aug;29(4):213-27. doi: 10.1007/s10565-013-9247-0.* Epub 2013 Jun 8.

Perbellini, L *et al.* 1991. Acute trichloroethylene poisoning by ingestion: clinical and pharmacokinetic aspects. *Intensive Care Med. 17(4):234-5. doi: 10.1007/BF01709883.*

Pereira, P *et al.* 2014. DNA damage induced by hydroquinone can be prevented by fungal detoxification. *Toxicol Rep. Nov 4;1:1096-1105. doi: 10.1016/j.toxrep.2014.10.024. eCollection*

2014.

Perera, FP. 1996. Molecular epidemiology: insights into cancer susceptibility, risk assessment, and prevention. *J Natl Cancer Inst. Apr 17;88(8):496-509. doi: 10.1093/jnci/88.8.496.*

Pesch, B *et al.* 2000. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. *International J. Epidemiology. 28(2):238-247. 10.1093/ije/29.2.238.* https://doi.org/10.1093/ije/29.2.238.

Philip, BK *et al.* 2007. Impact of repeated exposure on toxicity of perchloroethylene in Swiss Webster mice. *Toxicology. Mar 22;232(1-2):1-14. doi: 10.1016/j.tox.2006.12.018*. Epub 2006 Dec 22.

Poli, D *et al.* 2022. Sex difference and benzene exposure: does it matter? *Int J Environ Res Public Health. Feb 18;19(4):2339. doi: 10.3390/ijerph19042339.*

Prout, MS *et al*. 1985. Species differences in response to trichloroethylene. I. Pharmacokinetics in rats and mice. *Toxicol Appl Pharmacol. Jul;79(3):389-400. doi: 10.1016/0041-008x(85)90137-1.*

Raaschou-Nielsen, O *et al.* 2003. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. *Am J Epidemiol. Dec 15;158(12):1182-92. doi: 10.1093/aje/kwg282.*

Reichert, D *et al.* 1983. Mutagenicity of dichloroacetylene and its degradation products trichloroacetyl chloride, trichloroacryloyl chloride and hexachlorobutadiene. *Mutat Res. Apr;117(1-2):21-9. doi: 10.1016/0165-1218(83)90149-0.*

Ripp, SL *et al.* 1997. Oxidation of cysteine S-conjugates by rabbit liver microsomes and cDNA-expressed flavin-containing mono-oxygenases: studies with S-(1,2-dichlorovinyl)-L-cysteine, S-(1,2,2-trichlorovinyl)-L-cysteine, S-allyl-L-cysteine, and S-benzyl-L-cysteine. *Mol Pharmacol. Mar;51(3):507-15.*

Robertson, ML *et al.* 1991. Two benzene metabolites, catechol and hydroquinone, produce a synergistic induction of micronuclei and toxicity in cultured human lymphocytes. *Mutat Res. Jul;249(1):201-9. doi: 10.1016/0027-5107(91)90147-g.*

Rosenfeld, PE *et al.* 2024. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955 to 1987. *Water, Air & Soil Pollution. 235(2):124. 10.1007/s11270-023-06863-y.* https://doi.org/10.1007/s11270-023-06863-y

Ross, D. 2000. The role of metabolism and specific metabolites in benzene-induced toxicity: evidence and issues. *J Toxicol Environ Health A. Nov;61(5-6):357-72. doi: 10.1080/00984100050166361.*

Ross, D. 1996. Metabolic basis of benzene toxicity. *Eur J Haematol Suppl. 60:111-8. doi: 10.1111/j.1600-0609.1996.tb01656.x.*

Ross, D *et al.* 1990. Activation and deactivation of quinones catalyzed by DT-diaphorase. Evidence for bioreductive activation of diaziquone (AZQ) in human tumor cells and detoxification of benzene

metabolites in bone marrow stroma. *Free Radic Res Commun. 8(4-6):373-81. doi: 10.3109/10715769009053371.*

Rothman, KJ and S Greenland. 1998. Causation and causal inference. In: *Modern Epidemiology. 2nd Edition. Lippincott Williams & Wilkins (eds.). Philadelphia. Chapter 2.*

Rothman, N *et al.* 1998. Urinary excretion of phenol, catechol, hydroquinone, and muconic acid by workers occupationally exposed to benzene. *Occup Environ Med. Oct;55(10):705-11. doi: 10.1136/oem.55.10.705.*

Ruckart, PZ *et al.* 2015. Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: a case control study. E*nviron Health. Sep 16;14:74. doi: 10.1186/s12940-015-0061-4.*

Rusyn, I *et al*. 2014. Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. *Pharmacol Ther. Jan;141(1):55-68. doi: 10.1016/j.pharmthera.2013.08.004*. Epub 2013 Aug 23.

Sabadie, N *et al.* 1980. Comparison of the hydroxylation of benzo(a)pyrene with the metabolism of vinyl chloride, N-nitrosomorpholine, and N-nitroso-N'-methylpiperazine to mutagens by human and rat liver microsomal fractions. *Cancer Res. Jan;40(1):119-26.*

Sabourin, PJ *et al.* 1987. Effect of dose on the absorption and excretion of [14C]benzene administered orally or by inhalation in rats and mice. *Toxicol Appl Pharmacol. Feb;87(2):325-36. doi: 10.1016/0041-008x(87)90294-8.*

Salmon, AG. 1976. Cytochrome P-450 and the metabolism of vinyl chloride. *Cancer Lett. Nov;2(2):109-13. doi: 10.1016/s0304-3835(76)80019-5.*

Sato, A *et al.* 1975. Kinetic studies on sex difference in susceptibility to chronic benzene intoxication--with special reference to body fat content. *Br J Ind Med. Nov;32(4):321-8. doi: 10.1136/oem.32.4.321.*

Schindler, J *et al.* 2007. The effect of genetic polymorphisms in the vinyl chloride metabolic pathway on mutagenic risk. *J Hum Genet. 52(5):448-455. doi: 10.1007/s10038-007-0134-5.* Epub 2007 Mar 24.

Schoenberg, JB *et al.* 1984. Case-control study of bladder cancer in New Jersey. I. Occupational exposures in white males. *J Natl Cancer Inst. May;72(5):973-81.*

Schumann, AM *et al.* 1980. The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. *Toxicol Appl Pharmacol. Sep 15;55(2):207-19. doi: 10.1016/0041-008x(80)90082-4.*

Seiji, K *et al.* 1989. Dose-excretion relationship in tetrachloroethylene-exposed workers and the effect of tetrachloroethylene co-exposure on trichloroethylene metabolism. *Am J Ind Med. 16(6):675-84.*

doi: 10.1002/ajim.4700160607.

Seldén, AI and G Alborg, Jr. 2011. Cancer morbidity in Swedish dry-cleaners and laundry workers: historically prospective cohort study. *Int Arch Occup Environ Health. Apr;84(4):435-43. doi: 10.1007/s00420-010-0582-7*. Epub 2010 Oct 1.

Sexton, K. 1997. Sociodemographic aspects of human susceptibility to toxic chemicals: Do class and race matter for realistic risk assessment? *Environ Toxicol Pharmacol. Dec;4(3-4):261-9. doi: 10.1016/s1382-6689(97)10020-5.*

Seyyedsalehi MS *et al*. 2024. Occupational benzene exposure and risk of kidney and bladder cancers: a systematic review and meta-analysis. *Eur J Cancer Prev. Aug 20. doi: 10.1097/CEJ.0000000000000911.*

Shala, NK *et al.* 2023. Exposure to benzene and other hydrocarbons and risk of bladder cancer among male offshore petroleum workers. *Br J Cancer. Sep;129(5):838-851. doi: 10.1038/s41416-023-02357-0.* Epub 2023 Jul 18.

Silver, SR *et al* 2014. Retrospective cohort study of a microelectronics and business machine facility. *Am J Ind Med. Apr;57(4):412-24. doi: 10.1002/ajim.22288*. Epub 2013 Dec 24.

Skender, LJ *et al.* 1991. A comparative study of human levels of trichloroethylene and tetrachloroethylene after occupational exposure. *Arch Environ Health. May-Jun;46(3):174-8. doi: 10.1080/00039896.1991.9937446.*

Snyder, CA *et al.* 1980. The inhalation toxicology of benzene: incidence of hematopoietic neoplasms and hematotoxicity in ARK/J and C57BL/6J mice. *Toxicol Appl Pharmacol. Jun 30;54(2):323-31. doi: 10.1016/0041-008x(80)90202-1.*

Snyder, CA *et al.* 1988. The carcinogenicity of discontinuous inhaled benzene exposures in CD-1 and C57Bl/6 mice. *Arch Toxicol. 62(5):331-5. doi: 10.1007/BF00293618.*

Steineck G *et al*. 1990. Increased risk of urothelial cancer in Stockholm during 1985-87 after exposure to benzene and exhausts. *Int J Cancer. Jun 15;45(6):1012-7. doi: 10.1002/ijc.2910450605.*

Swanson, GM and PB Burns. 1995. Cancer incidence among women in the workplace: a study of the association between occupation and industry and 11 cancer sites. *J Occup Environ Med. Mar;37(3):282-7. doi: 10.1097/00043764-199503000-00002.*

Tauber, J. 1970. Instant benzol death. *J Occup Med. Mar;12(3):91-2.*

Til, HP *et al.* 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol. Oct;29(10):713-8. doi: 10.1016/0278-6915(91)90130-y.*

Travier, N *et al.* 2002. Cancer incidence of dry cleaning, laundry and ironing workers in Sweden. *Scand J Work Environ Health. Oct;28(5):341-8. doi: 10.5271/sjweh.684.*

Turkall, RM *et al.* 1988. Soil adsorption alters kinetics and bioavailability of benzene in orally exposed male rats. *Arch Environ Contam Toxicol. Mar;17(2):159-64. doi: 10.1007/BF01056020.*

Ungváry, G *et al*. 1978. Effects of vinyl chloride exposure alone and in combination with trypan blue--applied systematically during all thirds of pregnancy on the fetuses of CFY rats. *Toxicology. Sep;11(1):45-54. doi: 10.1016/s0300-483x(78)90389-x.*

Valentine, JL *et al*. 1996. Reduction of benzene metabolism and toxicity in mice that lack CYP2E1 expression. *Toxicol Appl Pharmacol. Nov;141(1):205-13. doi: 10.1006/taap.1996.0277.*

Vamvakas, S *et al.* 1989a. Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine S-conjugates of haloalkenes and haloalkanes. *Mutat Res. Apr;222(4):329-35. doi: 10.1016/0165-1218(89)90108-0.*

Vamvakas, S *et al.* 1989b. Genotoxicity of haloalkene and haloalkane glutathione S-conjugates in porcine kidney cells. *Toxicol In Vitro. 3(2):151-6. doi: 10.1016/0887-2333(89)90058-1.*

Vamvakas, S *et al.* 1989c. Mutagenicity of tetrachloroethene in the Ames test--metabolic activation by conjugation with glutathione. *J Biochem Toxicol. Spring;4(1):21-7. doi: 10.1002/jbt.2570040105.*

Vamvakas, S *et al.* 1988. Induction of unscheduled DNA synthesis and micronucleus formation in Syrian hamster embryo fibroblasts treated with cysteine S-conjugates of chlorinated hydrocarbons. *Cell Biol Toxicol. Dec;4(4):393-403. doi: 10.1007/BF00117768.*

Van Duuren, BL *et al* 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J Natl Cancer Inst. Dec;63(6):1433-9.*

Varshavsky, JR *et al.* 2023. Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. *Environ Health. Jan 12;21(Suppl 1):133. doi: 10.1186/s12940-022-00940-1.*

Vogel, TM and PL McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. *Appl Environ Microbiol. May;49(5):1080-3. doi: 10.1128/aem.49.5.1080-1083.1985.*

Völkel, W and W Dekant. 1998. Chlorothioketene, the ultimate reactive intermediate formed by cysteine conjugate beta-lyase-mediated cleavage of the trichloroethene metabolite S-(1,2-Dichlorovinyl)-L-cysteine, forms cytosine adducts in organic solvents, but not in aqueous solution. *Chem Res Toxicol. Sep;11(9):1082-8. doi: 10.1021/tx980084d.*

Wagoner, JK. 1983. Toxicity of vinyl chloride and poly(vinyl chloride): a critical review. *Environ Health Perspect. Oct;52:61-6. doi: 10.1289/ehp.835261.*

Wang, L *et al.* 2017. Genetic polymorphism analysis of cytochrome P4502E1 (CYP2E1) in a Chinese Tibetan population. *Medicine (Baltimore). Nov;96(47):e8855. doi:*

10.1097/MD.0000000000008855.

Watanabe, PG *et al.* 1978. Comparison of the fate of vinyl chloride following single and repeated exposure in rats. *Toxicol Appl Pharmacol. May;44(2):391-9. doi: 10.1016/0041-008x(78)90199-0.*

Watanabe, PG *et al.* 1976. Fate of (14C)vinyl chloride after single oral administration in rats. *Toxicol Appl Pharmacol. May;36(2):339-52. doi: 10.1016/0041-008x(76)90013-2.*

Werner, M *et al*. 1996. Sulfoxidation of mercapturic acids derived from tri- and tetrachloroethene by cytochromes P450 3A: a bioactivation reaction in addition to deacetylation and cysteine conjugate beta-lyase mediated cleavage. *Chem Res Toxicol. Jan-Feb;9(1):41-9. doi: 10.1021/tx950075u.*

Wilbur, S *et al.* 2008. ATSDR evaluation of health effects of benzene and relevance to public health. *Toxicol Ind Health. Jun-Jul;24(5-6):263-398. doi: 10.1177/0748233708090910.*

Wilson, R and EA Crouch. 1987. Risk assessment and comparisons: an introduction. *Science. Apr 17;236(4799):267-70. doi: 10.1126/science.3563505.*

Wilson, RT *et al.* 2008. Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden. *Am J Ind Med. Feb;51(2):83-99. doi: 10.1002/ajim.20522.*

Winek, CL and WD Collom. 1971. Benzene and toluene fatalities. *J Occup Med. May;13(5):259-61.*

Winek, CL *et al.* 1967. Fatal benzene exposure by glue-sniffing. *Lancet. Mar 25;1(7491):683. doi: 10.1016/s0140-6736(67)92578-0.*

Withey, JR. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. *J Toxicol Environ Health. Jan;1(3):381-94. doi: 10.1080/15287397609529338.*

Wrenn, K. 1990. Dysuria, frequency, and urgency. In: *Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd Edition*. Walker HK, Hall WD, Hurst JW, editors. Boston: Butterworth Publishers, a division of Reed Publishing. Chapter 181

Xie, S *et al*. 2024. Occupational exposure to organic solvents and risk of bladder cancer. *J Expo Sci Environ Epidemiol. May;34(3):546-553. doi: 10.1038/s41370-024-00651-4.* Epub 2024 Feb 16.

Yager, JW *et al.* 1990. Characterization of micronuclei induced in human lymphocytes by benzene metabolites. *Cancer Res. Jan 15;50(2):393-9.*

Yoshida, M *et al.* 1996. Concentrations of trichloroethylene and its metabolites in blood and urine after acute poisoning by ingestion. *Hum Exp Toxicol. Mar;15(3):254-8. doi: 10.1177/096032719601500312.*

Yu, R and CP Weisel. 1996. Measurement of benzene in human breath associated with an environmental

exposure. *J Expo Anal Environ Epidemiol. Jul-Sep;6(3):261-77.*

Zhang, X *et al*. 2020. Influence of benzene exposure, fat content, and their interactions on erythroid-related hematologic parameters in petrochemical workers: a cross-sectional study. *BMC Public Health. Mar 23;20(1):382. doi: 10.1186/s12889-020-08493-z.*

Zhao, Y *et al.* 2005. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. *Am J Ind Med. Oct;48(4):249-58. doi: 10.1002/ajim.20216.*

APPENDIX A: Curriculum Vita

CURRICULUM VITAE

Laura M. Plunkett, Ph.D., D.A.B.T

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Houston, TX 77077

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

Partner. BioPolicy Solutions LLC, June 2020 – present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Registered Patent Agent Licata & Tyrrell, P.C., Marlton, N.J., 1999 – 2023
Assists clients with obtaining patent protection, specializing in products used in medical applications (drugs, devices, dietary supplements). Assists clients with developing regulatory strategies for commercialization of their inventions. Provides regulatory support for companies engaged in manufacturing and marketing of products regulated by the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency and other regulatory bodies in the U.S. and worldwide.

President. Integrative Biostrategies (IB) LLC, 2001- May 2020
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia,

College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Registered patent agent, 1999 [Registration No. 45,015]
Diplomate, American Board of Toxicology, 1993 to present.

ACADEMIC AFFILIATION

Adjunct Professor. Baylor University, Department of Environmental Science, 2017-present

PROFESSIONAL MEMBERSHIPS

Member, Society of Toxicology 1992 – present

President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2021-2022

Vice-President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2020-2021

Vice-President Elect, Society of Toxicology Risk Assessment Specialty Section (RASS) 2019-2020

Councilor, Society of Toxicology Ethical, Legal, Forensic and Societal Issues Specialty Section (ELFSI) 2023-present

Member, Lone Star Chapter Society of Toxicology 2007 – present

Councilor, Lone Star Chapter Society of Toxicology 2010 - 2013

Secretary, Lone Star Chapter Society of Toxicology 2013 – 2015

Vice President, Lone Star Chapter Society of Toxicology 2015-2016

President, Lone Star Chapter, Society of Toxicology 2016-2017

Past President, Lone Star Chapter, Society of Toxicology 2017-2018

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Councilor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Regulatory Affairs Professionals Society, 2003 - present

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 – present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 – present

Member, International Association of Plumbing and Mechanical Officials (IAPMO) Committee Z1123 (Prop 65) Committee, 2020 - present

PUBLICATIONS

1. Bobst, S, Ryan, K, **Plunkett, LM,** Willett, KL. 2020. ToxPoint: Toxicology studies on Δ9-tetrahydrocannabinol and cannabidiol-containing products available to consumers are lacking. *Toxicol. Sci.* 178:1-2.

2. Rajendran, N, Seagrave, JC, **Plunkett, LM**, MacGregor, JA. A comparative assessment of the acute inhalation toxicity of vanadium compounds. *Inhal. Toxicol.* 2016. 28:618-628.

3. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well can in vitro data predict in vivo effects of chemicals? Rodent carcinogenicity as a case study. *Regul. Toxicol. Pharmacol.* 2016. 77:54-64.

4. **Plunkett, LM**, Kaplan, AM, Becker, RA. Challenges in using the ToxRefDB as a resource for toxicity modeling. *Regul. Toxicol Pharmacol*. 2015. 72:610-614.

5. **Plunkett, LM**, Becker, RA, Kaplan, M. An enhanced tiered toxicity testing framework with triggers for assessing hazards and risks of commodity chemicals.

Regul. Toxicol. Pharmacol. 2010. 58:382-394.

6. Chambers, A, Krewski, D, Birkett, N, **Plunkett, L,** Hertzberg, R, Danzeisen, R, Aggett, PJ, Starr, TB , Baker, S, Dourson, M, Jones, P, Keen, CL , Meek, B, Schoeny, R, and Slob, W *J.* An exposure-response curve for copper excess and deficiency. *Toxicol. Environ. Health.* 2010. 13:546- 578.

7. Krewski, D, Chambers, A, Stern, BA, Aggett, PA, **Plunkett, L,** Rudenko, L. Development of a copper database for exposure-response analysis. *J. Toxicol. Environ. Health.* 2010. 73:208-216.

8. **Plunkett, LM**, Becker, RA. Does the standard toxicological testing paradigm for industrial chemicals apply to screening for children's health risks? *The Open Toxicol. J.* 2008, 2:42-60.

9. Becker, RA, **Plunkett, LM**, Borzelleca, JF, Kaplan, AM. Tiered toxicity testing: Evaluation of toxicity-based decision triggers for human health hazard characterization. *Food Chem. Toxicol*. 2007, 45:2454-2469.

10. MacGregor, JA, **Plunkett, LM**, Youngren, SH, Manley, A, Plunkett, JB, Starr, TB. Humans Appear No More Sensitive than Laboratory Animals to the Inhibition of Red Blood Cell Cholinesterase by Dichlorvos (DDVP). *Regul. Toxicol. Pharmacol*., 2005, 43:150-167.

11. **Plunkett, LM.** Do current FIFRA guideline tests protect infants and children? Lead as a case study. *J Regul Toxicol Pharmacol* 1999;29:80-87.

12. **Plunkett, LM,** Seifen E, Kennedy RH. Effect of morphine pretreatment on cocaine cardiotoxicity in anesthetized guinea pigs. *Arch Int Pharmacodyn* 1989;297:60-67.

13. Zorbas M., Owens SM, **Plunkett LM,** Bui H. The pharmacokinetics of [3H]-[1-(2-thienyl)cyclohexyl]piperidine (TCP) in Sprague Dawley rats. *J Drug Metab Disposit* 1989;17:641-645.

14. Seifen E, **Plunkett LM,** Kennedy RH. Cardiovascular and lethal effects of cocaine in anesthetized dogs and guinea pigs. *Arch Int Pharmacodyn* 1989;300:241-253.

15. McCarty R, **Plunkett LM.** Regulation of binding sites for atrial natriuretic factor (ANF) in rat brain. *Peptides* 1988;9(S1):3-8.

16. Stewart RE, Swithers SE, **Plunkett LM,** McCarty R. ANF receptors: distribution and regulation in central and peripheral tissues. *Neurosci Biobehav Rev* 1988;12:151-168.

17. **Plunkett LM,** Tackett RL. Central dopamine receptors and their role in digoxin-induced cardiotoxicity in the dog. *J Pharm Pharmacol* 1987;39:29-34.

18. **Plunkett LM,** Tackett RL. Increases in CSF norepinephrine associated with the onset of cardiac glycoside toxicity. *Eur J Pharmacol* 1987;136:119-122.

19. McCarty R, **Plunkett LM.** Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. *Brain Res Bull* 1987;18:289-94.

20. **Plunkett LM,** Shigematsu K, Kurihara M, Saavedra JM. Localization of angiotensin II receptors along the anteroventral-third ventricle area of the rat brain. *Brain Res* 1987;405:205-212.

21. Israel A, **Plunkett LM,** Saavedra JM. Increased number of angiotensin II binding sites determined by autoradiography in anterior pituitary of water deprived and Brattleboro rats. *Neuroendocrinol* 1986;42:57-63.

22. Saavedra JM, Correa FMA, **Plunkett LM,** Israel A, Kurihara M, Shigematsu K. Angiotensin and atrial natriuretic peptide binding in brain of hypertensive rats. *Nature* 1986;320:758-760.

23. McCarty RM, **Plunkett LM.** Forebrain atriopeptin binding sites: Alterations in spontaneously hypertensive rats. *Neurochem Int* 1986;9:177-183.

24. Shigematsu K, Saavedra JM, **Plunkett LM,** Kurihara M, Correa FMA. Angiotensin II binding sites in the anteroventral-third-ventricle (AV3V) area and related structures of the rat brain. *Neurosci Lett* 1986 67:37-41.

25. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative distribution of angiotensin-converting enzyme (kininase II) in discrete areas of the rat brain by autoradiography with computerized microdensitometry. *Brain Res* 1986;275:259-266.

26. Saavedra JM, Israel A, **Plunkett LM,** Kurihara M, Shigematsu K, Correa FMA. Quantitative distribution of angiotensin II binding sites in rat brain by autoradiography. Peptides 1986;7:679-687.

27. McCarty R, **Plunkett LM**. Binding sites for atrial natriuretic factor (ANF) in brain: alterations in Brattleboro rats. *Brain Res Bull* 1986;17:767-772.

28. **Plunkett LM,** Gokhale RD, Vallner JJ, Tackett RL. Prazosin alters free and total plasma digoxin in dogs. *Am Heart J* 1985;109:847-851.

29. **Plunkett LM,** Tackett RL. The effects of central beta-receptor antagonism on digoxin cardiotoxicity. *Res Comm Chem Path Pharmacol* 1985;48:209-220.

30. Israel A, Saavedra JM, **Plunkett L.** Water deprivation upregulates angiotensin II receptors in rat anterior pituitary. *Am J Physiol* 1985;248 (Endocrino. Metabl. II):E264-E267.

31. Niwa M, Shigematsu K**, Plunkett L,** Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. *Am J Physiol* 1985;249 (Heart Circ. Physiol 18):H694-H697.

32. Correa FMA, **Plunkett LM,** Saavedra JM, Hichens M. Quantitative autoradiographic determination of angiotensin-converting enzyme (kininase II) kinetics in individual rat brain nuclei with 125I-351A, a specific enzyme inhibitor. *Brain Res* 1985;347:192-195.

33. Israel A, Niwa M, **Plunkett LM,** Saavedra JM. High affinity angiotensin receptors in rat adrenal medulla. *Regul Pept* 1985;11:237-243.

34. Israel A, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic characterization of receptors for angiotensin II and other neuropeptides in individual brain nuclei and peripheral tissues from single rats. *Cell Mol Neurobiol* 1985;5:211-222.

35. **Plunkett LM,** Correa FMA, Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme kinetics in rat pituitary and adrenal glands with 125I-135A, a specific inhibitor. Regul Pept 1985;12:1-10.

36. **Plunkett LM,** Saavedra JM. Increased angiotensin II binding affinity in the nucleus tractus solitarius of spontaneously hypertensive rats. *Proc Natl Acad Sci* 1985;82:7721-7724.

37. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digoxin cardiotoxicity. *J Pharmacol Exp Ther* 1983;227:683-686.

ABSTRACTS

1. **Plunkett, L.M.** Neuropharmacological Drugs and Impairment: Not So Simple to Define. Society of Toxicology annual meeting, March 10-14, 2024, Salt Lake City, UT.
2. **Plunkett, L.**M. ROUNDTABLE. Women's Health on the Frontlines: Science Behind

Sex-Specific Toxicology Differentials, Health Disparity, and Marginalization and their Ethical Implications. Society of Toxicology annual meeting, March 10-14, 2024, Salt Lake City, UT.

3. Woodall, G.M., Grimm, F.A, Pechacek, N., Wignall, J., Minsavage, G.D. and **Plunkett, L.M.** Risk Assessment Syllabus. Society of Toxicology annual meeting, March 19-23, 2023, Nashville, TN.

4. **Plunkett, L.M.** Cannabidiol Incorporation into Consumer Products in the US: Regulatory Challenges to Commercialization. Presenting at the Society of Toxicology annual meeting. March 25, 2021. Virtual Meeting.

5. **Plunkett, LM**. Cannabidiol Incorporation into Consumer Products in the US: Regulatory Challenges to Commercialization. Presenting at the annual meeting of the American Association for the Advancement of Science (AAAS), February 8-11, 2021. Virtual meeting

6. **Plunkett, LM**. Marijuana and Public Safety Concerns: States in Charge. Presenting at Society of Toxicology annual meeting. March 11-15, 2018, San Antonio, Texas.

7. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well do High Throughput Screening (HTS) assay data predict in vivo rodent carcinogenicity of pesticides? Presenting at Society for Risk Analysis annual meeting, December 11-15, 2016, San Diego, California.

8. **Plunkett, LM**. THC and legal issues related to the state of the science. Symposium presenter at the Society of Toxicology, New Orleans, LA, March 2016.

9. Goyak, K, Alyea, R, Becker, RA, **Plunkett, LM**, Plunkett, JB. Evaluating the ability of high-throughput screening (HTS) assays to capture the biological activity of industrial chemicals. Poster presentation at the Society of Toxicology, New Orleans, LA, March 2016.

10. MacGregor, JA, Plunkett, JB, **Plunkett, LM.** The occurrence of chemically induced lung tumors in rodents as an outcome in NTP chronic bioassays and the impact on cancer classifications. Presented at the Society of Toxicology, San Diego, CA, March 2015.

11. Urban, JD, Thompson, CM, **Plunkett, LM**, Perry, C, Haws, LC. A state of the science of copper reference dose for soil remediation. Presented at the Society of Toxicology, San Diego, CA, March 2015.

12. **Plunkett, LM**, Kaplan, AM, Becker, RA. Evaluation of a tiered toxicity testing decision trigger for assessing reproductive hazards of commodity chemicals.

Submitted for presentation at the Society of Toxicology, Phoenix, AZ, March 2014.

13. **Plunkett, L.M.** Overview of key public and worker health concerns in Texas food production. Presented at the Society of Toxicology, San Antonio, TX, March 2012.

14. **Plunkett, L.M.**, Starr, T.B., MacGregor, J.A., Manley, A. Corn oil as a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice exposed by gavage. Presented at Society of Toxicology, Washington, D.C., March 9, 2011. [Award received for "Best Presentation"]

15. **Plunkett, LM**, MacGregor, JA, Starr, TB, Manley, A. Daily gavage with corn oil is a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice. Toxicology Lett. 189S:S142. Presented at EUROTOX, Dresden, Germany, September 14, 2009.

16. **Plunkett, LM**, MacGregor, JA, Starr, TB, Youngren, SH, Manley, A. Determination of a dichlorvos-specific acute interspecies uncertainty factor. Society of Toxicology, Seattle, WA, March 19, 2008.

17. **Plunkett, LM**, Starr, TB, Youngren, SH, MacGregor, JA, Manley, A. Determination of the magnitude of intraspecies differences in red blood cell cholinesterase inhibition in response to dichlorvos exposure. Society of Toxicology, San Diego, CA, March 6, 2006.

18. **Plunkett, LM**, Licata, JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Orlando, FL, March 4, 2006.

19. **Plunkett, LM,** Licata JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Phoenix, AZ February 2005.

20. **Plunkett, LM**. Qualitative Interpretation of Complex and Disparate Data Sets for Dose-Response Assessment of Essential Trace Elements: Copper as a Case Study. Society for Toxicology, Baltimore, MD March 2004 .

21. **Plunkett, LM.** Evaluating qualitative and quantitative dose-response data in complete data sets for comparative dose-response assessment. Soc. Risk Analysis, Baltimore, MD, December 10, 2003.

22. **Plunkett, LM**, Rieth S, Starr T. Issues in assessing risks for cholinesterase-inhibiting pesticides: A decision tree approach. Soc. Risk Analysis, New Orleans, LA, December 9-12, 1996

23. **Plunkett, LM**, Brown S. Assessment of the potential neuropathic risk to banana workers from dermal exposure to chlorpyrifos. Soc. Risk Analysis, Honolulu, HI, December 3-7, 1995

24. **Plunkett, LM**, Russell K. Cooperation versus Confrontation: Reconciling Lead regulations, exposure studies, and public perception. SEGH Conference, July, Salt Lake City, UT, 1994

25. **Plunkett LM**, Wixtrom RN, Cabrera CR. Evaluation of the long-term safety of inflatable penile prostheses: a critical analysis of potential carcinogenic, reproductive, teratogenic, or adverse immunological effects of silicone. Western Section of American Urological Association Meeting, Seattle, WA, August 21-25, 1994

26. Wixtrom RN, **Plunkett LM**, Clarkin CM. Complications of inflatable penile prostheses: A comprehensive review of infection, mechanical complications, erosion/migration/extrusion, and fibrous capsule formation. 1994.

27. Wixtrom RN, Clarkin CM, Purkait B, **Plunkett LM**. A review of clinical experience with the Mentor Alpha I and Mark II inflatable penile prostheses. 1994.

28. **Plunkett LM**, Rosolowsky LJ, Lerner DM, Washburn ST. A biokinetic model for predicting blood lead levels in adults living near a former battery recycling facility. SEGH Conference, New Orleans, LA, July, 1993.

29. Rosolowsky LJ, Edelmann KG, **Plunkett LM**. A biokinetic model for predicting blood lead levels in adults that accounts for intermittent exposures. Society for Risk Analysis, December, 1993

30. **Plunkett LM**, Owens SM , Gunnell M, Owens RB. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) dosing on [3H]TCP and [3H] haloperidol binding in rat brain. *FASEB J* 1990;4:A329.

31. Owens RB, Owens SM, Gunnell M, **Plunkett LM**. 1990. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) on lymphocyte in subsets in rats. *FASEB J* 1990;4:A337.

32. Zorbas M, Owens SM, **Plunkett LM**, Bui H. [3H]TCP protein binding and pharmacokinetics in Sprague-Dawley rat. *FASEB J* 1989;3:A1036.

33. **Plunkett LM**, Kennedy RH, Seifen E. Effects of chronic stress on myocardial beta-adrenergic receptor binding. *The Pharmacologist* 1988;A1300.

34. Evans, R.E., **Plunkett LM**, Kennedy RH, Seifen E. [3H]Ouabain binding to regions of rat heart as determined by autoradiography. *The Pharmacologist* 1988;A41.

35. Massey BW, **Plunkett LM**, Kennedy RH, Seifen E. Alterations in brain angiotensin II binding in the aged rat. Soc. Neuroscience 1987 Abstracts, p. 722.

36. **Plunkett LM**, Alexander N, Saavedra JM. Altered angiotensin II binding in adrenal gland, pituitary gland and brain of sinoaortic denervated rats. Am. Soc. Hypertension. New York, NY, May 1986.

37. Saavedra JM, **Plunkett LM**, Correa FMA. Increased number of angiotensin II binding sites in the subfornical organ of spontaneously hypertensive rates. Am. Soc. Hypertension, New York, NY, May 1986.

38. **Plunkett LM**, Niwa M, Shigematsu K, Saavedra JM. Increased angiotensin II (ANG) binding in superior cervical ganglia of spontaneously hypertensive rats (SHR). *Fed. Proc* 1985;3: 498.

39. **Plunkett LM**, Saavedra JM. Discrete localization of angiotensin II (ANG) binding sites in rat brainstem by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, D.C., May, 1985.

40. **Plunkett LM**, Israel A, Niwa M, Shigematsu K, Saavedra JM. Alterations in angiotensin II binding in pituitary gland, adrenal gland and superior cervical ganglia of spontaneously hypertensive rats (SHR) as determined by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, DC, May 1985.

41. Shigematsu K, Niwa M, **Plunkett LM**, Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. Neural and Endocrine Peptide and Receptors, Symposium '85, Washington, DC, May 1985.

42. McCarty R, **Plunkett LM**, Israel A, Saavedra JM. Quantitation of somatostatin binding sites in rat brain. Neural and Endocrine Peptides and Receptors, Symposium '85, Washington, DC, May, 1985.

43. **Plunkett LM**, Saavedra JM. Increased angiotensin II (ANG) binding in brainstem nuclei of adult spontaneously hypertensive rats (SHR) by quantitative autoradiography. Interamerican Society of Hypertension, Cleveland, OH, May 1985.

44. Saavedra JM, **Plunkett LM**, Niwa M, Israel A, Shigematsu K, R. McCarty, Correa FMA. Autoradiographic-microdensitometric methods for the kinetic analysis of neuropeptide receptors and peptidases in individual brain nuclei. IVth World Congress of Biological Psychiatry, Philadelphia, PA, September, 1985.

45. **Plunkett LM** Saavedra JM. 1985. Altered angiotensin II binding in ganglia and brainstem nuclei of spontaneously hypertensive rats (SHR). Council for High Blood Pressure Research, Cleveland, OH, September 1985.

46. **Plunkett LM**, Correa FMA, Saavedra JM. Quantification of angiotensin-1-converting enzyme kinetics in individual rat pituitary and adrenal glands with 125I-MK351A, a specific enzyme inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

47. McCarty R**, Plunkett LM**, Shigematsu K, Saavedra JM. Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. Society for Neuroscience, Dallas, Texas, October, 1985.

48. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme distribution in rat brain with 125I-MK351A, a specific inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

49. **Plunkett LM,** Saavedra JM. Altered angiotensin II binding kinetics in brainstem, pituitary gland, and adrenal gland in adult SHR. 5th International Symposium on SHR and Related Studies, Tokyo, Japan, October, 1985.

50. **Plunkett LM,** Tackett RL. CSF catecholamine activity decreases during cardiac glycoside-induced arrhythmogenesis. *The Pharmacologist* 1985; 25:745.

51. Tackett RL**, Plunkett LM**. Naloxone inhibits the central hypotensive actions of propranolol. *The Pharmacologist* 1983;25:101.

52. **Plunkett LM,** Vallner JJ, Tackett RL. Prazosin lowers plasma digoxin levels. American Heart Assoc, pp 15, Savannah, GA, 1983.

53. Tackett RL**, Plunkett LM**. 1983. BHT 933 lowers blood pressure and increases cerebrospinal fluid norepinephrine levels. American Heart Assoc, pp 16, Savannah GA, 1983.

54. Bayoumi SM, Gokhale R, **Plunkett L,** Vallner JJ. Pharmacokinetics of clortrimazole in dogs. *Acad. Pharmaceut. Sci* 1983;13(2):204, (Miami meeting).

55. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digitalis cardiotoxicity. *The Pharmacologist* 1982; 24:489A.

56. **Plunkett LM,** Tackett RL. Central alpha antagonism decreases blood pressure in the dog. Proc. Soc. Exp. Biol. Med. S.E. Sec. 7:12A 1982.

PRESENTATIONS

1. **Plunkett, LM.** Reproductive Toxicology. Invited lecture at NYU, Department of Environmental Medicine. October 28, 2020.

2. **Plunkett, L.M.** Provided public comments at the FDA-sponsored public meeting on "Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc", February 4, 2020.

3. **Plunkett, L.M.** Pesticide Toxicology. Invited lecture at NYU, Department of Environmental Medicine. December 4, 2019.

4. **Plunkett, L.M.** Practical applications of risk assessment. Lecturer at University of Texas Medical Branch at Galveston, Department of Pharmacology and Toxicology. October 19, 2018.

5. **Plunkett, LM.** Non-obviousness and §103. Lecturer at Rutgers School of Law, Camden Campus. November 6, 2012.

6. **Plunkett, LM.** Regulatory primer for pharmacy students: focus on human therapeutics. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

7. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

8. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Drexel University School of Law. September 22 and 24, 2008.

9. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Rutgers School of Law, Camden Campus. September 22 and 24, 2008.

10. **Plunkett, LM.** Discussion of the Adequacy of Current Regulatory Risk Assessment Approaches for Protection of Children's Health and the Health of Other "Sensitive" Human Subpopulations. Testimony before the U.S. Senate Enviornment and Public Works Committee. April, 29, 2008.

11. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Florida A&M University, Tallahassee, FL, October 26, 2006.

12. **Plunkett, LM**. The guidance as currently implemented: experience with Minnesota's draft risk levels. Presented at the ISRTP workshop entitled: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures. Genotoxic Mode of Action and Implications for Human Health-Based Standards. Baltimore, MD February 10, 2005.

13. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 17, 2004.

14. **Plunkett, LM**. Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

15. **Plunkett, LM**. A Road map to the US Food And Drug Administration Regulations. Invited Speaker and Session Co-chair, Federation of European Biochemical Societies (FEBS), Istanbul, Turkey, October 20-24, 2002.

16. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 2001.

17. **Plunkett, LM** . Differences and Similarities Between Children and Adults in their Exposure and Response to Environmental Chemicals: An Update Since 1992. Invited Speaker at ToxForum, Aspen CO, July 2001.

18. **Plunkett, LM**. Do current FIFRA guideline tests protect infants and children? Lead as a case study. Invited speaker at the Sixteenth International Neurotoxicology Conference, Pesticides and Susceptible Populations: Who is at Risk and When? Little Rock, Arkansas, September 13-16 1998

19. **Plunkett, LM**. An overview of biotechnology regulations: the USFDA and the USEPA. Lecturer at University of Houston at Clearlake, October 16 1998.

20. Rodricks, JV, Santamaria, AB, **Plunkett, LM**. Risk Assessment as a Tool in Litigation: A Discussion of the Uses and Their Limits [Presented by **Plunkett LM**]. Society for Risk Analysis, , New Orleans, LA. December 10 1996.

21. **Plunkett, LM**. Current Issues in Lead Exposure and Risk Assessment. Symposia at the annual meeting of The American College of Toxicology, Valley Forge, PA. November 9 1996.

22. **Plunkett, LM** . An Overview of Biotechnology Regulations: Environmental Regulations. Lecturer at the South Texas School of Law, October 1995.

23. **Plunkett, LM**. An Overview of Biotechnology Regulations: FDA Regulations. Lecturer at the South Texas School of Law, October 1995.

24. **Plunkett, LM** . A Discussion of Toxicokinetics. Featured speaker at a symposium at the Int. Congress of Toxicol., July 5 1995.

25. **Plunkett, LM**. Chutes and Ladders: The Hazardous Journey for R&D to Market. Featured speaker at the Futurist's Conference, Irvine, CA, June 28, 1995.

BOOK CHAPTERS

1. Rudenko, L, **Plunkett, LM**, Kornum, A, Rocklinsberg, H, Sorensen, DB, Gjerris, M. 2024. An overview of the regulation of genetically altered animals in research. In: *Biotech Animals in Research: Ethical and Regulatory Aspects*. CRC Press: Boca Raton. Chapter 3.

2. Anderson, SA, **Plunkett, LM.** 2023. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

3. Anderson, SA, **Plunkett, LM.** 2022. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

4. Anderson, SA, **Plunkett, LM**. 2021. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

5. Anderson, SA**, Plunkett, LM.** 2020. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

6. Anderson, SA, **Plunkett, LM.** 2019. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

7. **Plunkett, LM**, O'Donnell, JT. 2016. Ketorolac abuse and injury in college athletics. In: *O'Donnell's Drug Injury, Fourth Edition*. O'donnell and O'Donnell (eds.), Lawyers & Judges Publishing Company, Inc: Tucson, AZ, pp. 591-602.

8. **Plunkett, LM,** Timmerman, LE. 2011. Pharmacovigilance and Postmarket Surveillance in the United States: The Role of the U.S. Food and Drug

Administration. In: Elements of Pharmacovigilance: Be Vigilant, Be Safe. R. Sehgal *et al.* (Eds.), Kongposh Publications: New Dehli.

9. Rodricks, JV, Frankos, VH, **Plunkett, LM**. 1995. Food Additives. In: Regulatory Toxicology. C.P. Chengelis, J.F. Holson and S.C. Gad (eds.) Raven Press, New York, New York, 51-82.

10. **Plunkett, LM**, Turnbull, D, Rodricks, JV. 1992. Differences between adults and children affecting exposure assessment. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment. P.S. Guzelian, C.J. Henry and S.S. Olin (eds.) ILSI Press, Washington D.C., 79-96.

11. Saavedra JM, **Plunkett LM**, Correa FMA, Israel A, Kurihara M, Shigematsu K. 1986. Quantitative autoradiography of angiotensin and atrial natriuretic factor binding sites in brain nuclei of spontaneously hypertensive rats. In Brain Peptides and Catecholamines in Cardiovascular Regulation in Normal and Disease States.

MISCELLANEOUS

1. **Plunkett LM.** 2008. U.S. Senate Committee on Environment & Public Works. Oral testimony. Full Committee hearing entitled "Oversight on EPA Toxic Chemical Policies". Tuesday, April 29, 2008.

2. **Plunkett LM**, Brett SM. 1991. A new look at lead: sources, exposures, and uptake in populations at risk. ENVIRON Report. 5:6-9.

3. **Plunkett LM**, Frankos VH. 1991. FDA re-examines the safety of silicone gel-filled breast implants. ENVIRON Report. 5:10-13.

APPENDIX B: Trial List

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT

Year	Case Name	Law Firm Represented
2019	*Forrest v. Johnson & Johnson (Talc)* *Trial Testimony* *06, 09-10 December 2019*	Beasley Allen (Montgomery, AL)
2019	*Crayton & Thibodeaux case (Taxotere)* *Deposition (**CONTINUATION**)* *13 December 2019*	David F. Miceli, LLC (Carrollton, GA)
2020	*McDermitt case* *Deposition* *21 January 2020*	Goldenberg Law, PLLC (Minneapolis, MN)
2020	*Benitez v. Dr. Ronald Seguar* *Deposition* *23 January 2020*	Orrill & Malbrough, LLC (Metairie, LA)
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *21 February 2020*	Baron and Budd (Encino, CA)
2020	*Kahn case (Taxotere)* *Deposition* *27 April 2020*	David F. Miceli, LLC (Carrollton, GA)
2020	*Sandra Sutter v. Cordis (IVC)* *Deposition* *27 May 2020 and 8 June 2020*	Blankenship Law Firm (Dallas, TX)
2020	*Roney v. Provient* *Deposition* *20 July 2020*	Smith, LaCien LLP (Chicago, IL)
2020	*Taxotere 505b2 Cases* *03 & 08 September 2020*	David F. Miceli, LLC (Carrollton, GA)

Year	Case Name	Law Firm Represented
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Trial* *26-27 October 2020*	Baron and Budd (Encino, CA)
2021	*Kahn case (Taxotere)* *Deposition* *7 April 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Cadigan v. Johnson & Johnson (Talc)* *Trial Testimony* *14-16 July 2021*	Beasley Allen (Montgomery, AL)
2021	*Talc MDL* *Deposition* *10 August 2021*	Ashcraft & Gerel LLP (Alexandria, VA) Beasley Allen (Montgomery, AL)
2021	*Kleiner v. Johnson & Johnson (Talc)* *Trial Testimony* *18-20 and 23-24 August 2021*	Beasley Allen (Montgomery, AL)
2021	*Geise et al. v. Johnson & Johnson (Talc)* *Trial Testimony* *10, 13-14 September 2021*	Beasley Allen (Montgomery, AL)
2021	*Guilbault and Plaisance v. 505b2 Defendants* *Deposition* *24 September 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Kahn v. Sanofi Aventis* *Trial Testimony* *12 November 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*State of New Mexico v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *19 November 2021*	Baron & Budd (Encino, CA)

Year	Case Name	Law Firm Represented
2021	*Mooneyham v. Bactolac* *9 December 2021*	Beasley Allen (Montgomery, AL)
2022	*Earnest case (Taxotere)* *Deposition* *01 June 2022*	David F. Miceli, LLC (Carrollton, GA)
2023	*Valsartan MDL* *Deposition* *12 January 2023*	Levin, Papantonio (Pensacola, FL) Hollis Firm (Kansas City, KS)
2023	*Valsartan MDL* *Deposition (continued)* *10 February 2023*	Levin, Papantonio (Pensacola, FL) Hollis Firm (Kansas City, KS)
2023	*Earnest case (Taxotere)* *Deposition (Continuation)* *28 March 2023*	Milberg Coleman (Knoxville, TN)
2023	*Norwood v. Albertson's Inc.* *Deposition* *17 May 2023*	Lundy. Soileau (Lake Charles, LA)
2023	*Jackson v. Bayer HealthCare Pharmaceuticals Inc., et al.,* *20 July 2023*	Yerrid Law (Tampa, FL)
2023	*State of Hawai'i (Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *29 August 2023*	Baron & Bud (Encino, CA)
2023	*State of Hawai'i (Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Trial* *25, 29 September and 2 October 2023*	Baron & Bud (Encino, CA)

Year	Case Name	Law Firm Represented
2023	*Blakely, et al v. Lifecell* *Deposition* *19 October 2023*	Cohen Malad (Indianapolis, IN)
2023	*Mississippi AG v. Johnson & Johnson (Talc)* *Deposition* *24 October 2023*	Beasley Allen (Montgomery, AL)
2024	*Hunt v. Covidien et al.* *Deposition* *25 January 2024*	Ferrar, Poirot, Feller & Daniel (Dallas, TX)
2024	*Seskin v. Johnson & Johnson (Talc)* *Trial* *13-14 February 2024*	Beasley Allen (Montgomery, AL)
2024	*Adams v. Covidien et al.* *Deposition* *28 February 2024*	Ferrar, Poirot, Feller & Daniel (Dallas, TX)
2024	*STRATTICE Hernia Mesh Litigation* *Trial* *8 March 2024*	Cohen & Malad LLP (Indianapolis, IN)
2024	*Maffthey v. Johnson & Johnson (Talc)* *Trial* *1-2 April 2024*	Beasley, Allen (Montgomery, AL)
2024	*JOSUE BERLANGA, et al.* *vs.* *BARNETT GATHERING, LLC, et al.* *Deposition* *23 April 2024*	Simon, Greenstone, Panatier (Dallas, TX)
2024	*JOSUE BERLANGA, et al.* *vs.* *BARNETT GATHERING, LLC, et al.* *Hearing* *9 May 2024*	Simon, Greenstone, Panatier (Dallas, TX)

Year	Case Name	Law Firm Represented
2024	*Lumaghi v. Covidien et al.* *Deposition* *13 June 2024*	Ferrar, Poirot, Feller & Daniel (Dallas, TX)
2024	*Holden v. Covidien et al.* *Deposition* *25 November 2024*	Ferrar, Poirot, Feller & Daniel (Dallas, TX)

APPENDIX C: List of Materials and Data Considered

[TO BE SUPPLIED]

APPENDIX D: Mixtures Cancer Risk Assessment for Oral Ingestion of Contaminated Water at Camp Lejeune

Use of EPA Guidance on Mixtures and Cancer Risk Assessment (EPA 1986; EPA 2000) to Estimate Risks Associated with Exposure to Contaminated Water at Camp LeJeune, North Carolina: Exposure Values Used Extracted[1] from ATSDR 2017

Chemical	Mean Water Level (mg/L)	Oral Dose Calculation (4L or 8L)/BW	Chemical Specific Oral CSF (risk/mg/kg bw-days)	Estimated Oral Cancer Risk	Inhalation Dose Calculation	Chemical Specific Inhalation IUR (risk per mg chemical/m^3 air)	Estimated Inhalation Cancer Risk	Total Estimated Cancer Risks/Chemical Across Routes
Calculated Based on Mean Values for Contaminant Levels in the Tarawa Terrace System (1975-1985)								
Trichloroethylene	0.003	6.59E-06 1.32E-05	4.60E-02	3.03E-07 6.07E-07				
Perchloroethylene	0.076	1.67E-04 3.34E-04	2.00E-03	3.34E-07 6.68E-07				
Vinyl Chloride	0.006	1.32E-05 2.64E-05	7.20E-01	9.49E-06 1.90E-05				
Benzene	Not reported		5.50E-02				--	--
Estimated Cancer Risk (oral)		1.87E-04 3.74E-04		1.01E-05 2.03E-05				
Calculated Based on Mean Values for Contaminant Levels in the Hadnot Point System (1975-1985)								
Trichloroethylene	0.359	7.89E-04 1.58E-03	4.60E-02	3.63E-05 7.26E-05				
Perchloroethylene	0.016	3.52E-05 7.03E-05	2.00E-03	7.03E-08 1.41E-07				
Vinyl Chloride	0.024	5.27E-05 1.05E-04	7.20E-01	3.80E-05 7.60E-05				
Benzene	0.005	1.10E-05 2.20E-05	5.50E-02	6.04E-07 1.21E-06				
Estimated cancer Risk (oral)		8.88E-04 1.78E-03		7.49E-05 1.50E-04				
Calculated Based on Mean Values for Contaminant Levels Across the Base (1975-1985)								
Trichloroethylene	0.181	3.98E-04 7.96E-04	4.60E-02	1.83E-05 3.66E-05				
Perchloroethylene	0.046	1.01E-04 2.02E-04	2.00E-03	2.02E-07 4.04E-07				
Vinyl Chloride	0.015	3.30E-05 6.59E-05	7.20E-01	2.37E-05 4.75E-05				
Benzene	0.005	1.10E-05 2.20E-05	5.50E-02	6.04E-07 1.21E-06				
Estimated Cancer Risk (oral)		5.43E-04 1.09E-03		4.28E-05 8.57E-05				

[1] Data were extracted from Tables 1a and 1b of ATSDR (2017) and reflect the mean values reported there for each chemical in water; exposure calculation was done that assumed ingestion of either 4 L or 8 L per day per person and an average body weight of 70 kg

***Equations used*:**

Cancer Risk = Dose (exposure) x CSF or IUR value

Dose (mg/kg bw/day) =(level in water (mg/L) x intake rate (liters per person per day) x 365 days/year) x [(365 days/year x 3 years) x 70 kg bw]-1

CSF and IUR values taken from ATSDR 2017 report for Camp LeJeune that referenced EPA

Oral CSF = risk per mg/kg bw-day

TCE Oral CSF = 4.6 E-2

PCE Oral CSF = 2 E-3

Vinyl chloride oral CSF = 7.2 E-1

Benzene oral CSF = 5.5 E-2

Inhalation IUR = risk per mg chemical/m^3 air

TCE IUR = 4.1 E-6

PCE IUR = 2.6 E-7

Vinyl chloride IUR = 4.4 E-6

Benzene IUR = 7.8 E-6

Estimated cancer risk per route (oral): based on EPA guidance (also ATSDR 2017), chemical-specific risk estimates were simply added