

# Exhibit 80

**GENERAL CAUSATION REPORT  
CAMP LEJEUNE WATER VOLATILE ORANGIC CHEMICALS  
AND BLADDER CANCER**


Prepared for:

Environmental Torts Litigation  
U.S. Department of Justice  
Washington, DC

February 7, 2025

Prepared by:

Michael J. McCabe, Jr., Ph.D.



---

**INTERTOX**

292 Main Street  
Suite 314  
Harleysville, PA 19438  
610.255.2171 phone  
[www.Intertox.com](http://www.Intertox.com)

## TABLE OF CONTENTS

1.0	INTRODUCTION .....	5
2.0	PURPOSE STATEMENT .....	5
3.0	SUMMARY OF OPINIONS .....	6
4.0	QUALIFICATIONS .....	7
5.0	METHODOLOGY .....	8
5.1	The Scientific Method and Bradford Hill Criteria .....	9
6.0	ANALYSIS AND BASIS OF OPINIONS .....	10
6.1	Volatile Organic Chemicals (VOCs) Identified at Camp Lejeune .....	10
6.1.1	TCE Toxicokinetics .....	11
6.1.2	PCE Toxicokinetics .....	12
6.1.3	Benzene Toxicokinetics .....	14
6.1.4	Vinyl Chloride Toxicokinetics .....	15
6.1.5	Genotoxic and Non-genotoxic Agents .....	17
6.2	Mechanisms of VOC Toxicity .....	18
6.2.1	Criticisms of Proposed Mechanisms of VOC Toxicity .....	20
6.2.1.1	Dr. Gilbert's Proposed Mechanisms .....	20
6.2.1.2	Dr. Bird's Proposed Mechanisms .....	20
6.2.1.3	Dr. Plunkett's Proposed Mechanisms .....	21
6.2.1.4	Dr. Hatten's Proposed Mechanisms .....	22
6.3	Overview of the Immune System .....	24
6.3.1	Innate and Adaptive Immunity .....	24
6.3.1.1	Innate Immunity .....	24
6.3.1.2	Adaptive Immunity .....	24
6.3.1.2.1	T Cell Subpopulations .....	25
6.4	Role of the Immune System in Cancer Development .....	27
6.4.1	Immunosurveillance .....	27

6.4.2	Inflammation.....	28
6.4.3	Oxidative Stress.....	29
6.4.4	Immunoediting.....	29
6.5	The Role of the Immune System in Bladder Cancer.....	31
6.5.1	Plaintiffs’ Experts’ Proposed Mechanistic Interconnections between TCE or Other VOCs and Bladder Cancer .....	36
6.6	Immunotoxicity.....	37
6.6.1	TCE Immunotoxicity .....	37
6.6.1.1	Human Studies.....	38
6.6.1.2	Summary of Human Studies on TCE Immunotoxicity.....	46
6.6.1.3	Animal Studies .....	47
6.6.1.4	Summary of Animal Studies on TCE Immunotoxicity.....	49
6.6.2	PCE Immunotoxicity.....	50
6.6.3	Benzene Immunotoxicity .....	53
6.6.4	Vinyl Chloride Immunotoxicity.....	55
7.0	CRITIQUE OF PLAINTIFFS’ EXPERT’S GENERAL CAUSATION OPINIONS.....	56
8.0	FINDINGS AND OPINIONS.....	60
9.0	COMPENSATION.....	62
10.0	EXHIBITS TO TESTIMONY.....	62
11.0	CASE-SPECIFIC DOCUMENTS REVIEWED .....	63
12.0	LITERATURE RESOURCES REVIEWED, CONSIDERED AND RELIED UPON .....	67
	APPENDIX A: CV OF MICHAEL J. MCCABE, JR., PH.D.....	78
	APPENDIX B: LIST OF PRIOR TESTIMONY FOR MICHAEL J. MCCABE, JR., PH.D. ....	94

## LIST OF FIGURES

FIGURE 1. METABOLISM OF TCE (LASH, 2025).....	13
FIGURE 2. METABOLISM OF PCE. (ATSDR 2019B) .....	15
FIGURE 3. METABOLISM OF BENZENE. ....	17
FIGURE 4. METABOLISM OF VINYL CHLORIDE.....	19
FIGURE 5. CD4+ T CELLS DEVELOPMENT AND THEIR FUNCTIONAL SUBSETS IN IMMUNITY (BASU ET AL., 2021).....	25
FIGURE 6. ROLES OF THE IMMUNE SYSTEM IN CANCER: FROM TUMOR INITIATION TO METASTATIC PROGRESSION (GONZALEZ ET AL., 2018) .....	29
FIGURE 7. THE LAYERS OF THE BLADDER WALL.....	30
FIGURE 8. LEFT, GRADING OF BLADDER CANCER BASED ON EXTENT OF INVASIVENESS (TA - T4). RIGHT TOP, BCG STIMULATION OF THE IMMUNE RESPONSE; RIGHT BOTTOM, IMMUNE CHECKPOINT THERAPEUTIC TARGETS (YANG ET AL., 2024). ....	32
FIGURE 9. POLARIZATION OF MACROPHAGE SUB-POPULATIONS IN BLADDER CANCER (JOSEPH & ENTING, 2019).....	33
FIGURE 10. CD4+ T CELL SUBTYPES AND TUMOR REGRESSION/PROGRESSION (BASU ET AL., 2021). ....	34

## LIST OF TABLES

TABLE 1. HUMAN STUDIES CONCERNING TCE IMMUNOTOXICITY.....	34
TABLE 2. SUMMARY OF HUMAN STUDIES REPORTING EFFECTS OF PCE ON CYTOKINES. ....	48

## **1.0 INTRODUCTION**

My report was prepared by request for the United States in the *Camp Lejeune Water Litigation*, Case No: 7-23-cv-897. The over-arching position of the plaintiffs is that their exposures to volatile organic compounds (VOCs) found in water several decades ago at Camp Lejeune caused them to suffer severe diseases, illnesses, injuries, and conditions, thereby affecting their quality of life or longevity. The VOCs at issue in this litigation are trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, and vinyl chloride (VC). The claimed pathways of exposure to the human body for these VOCs include ingestion, inhalation, and dermal contact. The current bellwether cases focus on five diseases: bladder cancer, kidney cancer, non-Hodgkin's lymphoma, leukemia, and Parkinson's Disease. This report focuses on bladder cancer. I have produced two other reports, one on kidney cancer and a combined NHL and leukemia report.<sup>1</sup>

## **2.0 PURPOSE STATEMENT**

Plaintiffs' expert, Dr. Kathleen Gilbert, expresses an opinion, amongst others, that TCE, PCE, benzene, and vinyl chloride alone, or in combination with one another, can cause bladder cancer through mechanisms that involve perturbations of the immune system or inflammatory processes. Other plaintiffs' experts have commented on the intersections between the Camp Lejeune VOCs, immunotoxicity, and bladder cancer in their reports. As is discussed in Dr. Julie Goodman's general causation report for bladder cancer, epidemiology evidence does not support a causal association between the VOCs and bladder cancer. Thus, the purpose of my investigation was to perform a complete, independent, and unbiased analysis to evaluate the VOCs' effects on the immune system to determine whether modulation of the immune system is a relevant mechanism by which the VOCs can cause bladder cancer. My analysis includes review, careful consideration, and, where warranted, critique of the opinions of plaintiffs' experts as expressed in their reports.

---

<sup>1</sup>Plaintiffs' experts, throughout their general causation reports, have expressed many duplicative opinions. I have attempted to address their opinions on bladder cancer as they relate to the scope of my analysis in this report. I incorporate the opinions expressed in my other two reports (Expert Report on Kidney Cancer of Michael J. McCabe, Jr., Ph.D. (dated February 7, 2025) and Expert Report on non-Hodgkin's Lymphoma and Leukemia of Michael J. McCabe, Jr., Ph.D. (dated February 7, 2025)) as if they were set out fully herein.

### 3.0 SUMMARY OF OPINIONS

I conclude the following:

Opinion 1: My independent analysis demonstrates that relevant animal and human studies do not show that modulation of the immune system is a plausible mechanistic pathway by which TCE, PCE, benzene, and vinyl chloride cause bladder cancer.

Opinion 2: Plaintiffs' expert, Dr. Kathleen Gilbert, has opined that TCE, PCE and benzene "causes immunotoxicity that can promote cancer development."<sup>2</sup> It is my opinion that Dr. Gilbert's novel opinion is without support and is merely a hypothesis that heretofore has not been adequately tested. The existing data and available scientific studies do not show that perturbations of the immune system or inflammatory processes by TCE, PCE, and benzene, alone or in combination with one another, are operant mechanistically as causes of bladder cancer. Hypothesis testing is a fundamental component of the scientific method. Leapfrogging over the necessity to test by adopting the mere hypothesis itself as conclusive, as Dr. Gilbert does, belies the purpose of engaging in the scientific method.

Opinion 3: Other plaintiffs' experts (e.g., Dr. Laura M. Plunkett and Dr. Steven B. Bird), neither of whom are immunologists, opined superficially that there is an intersection between Camp Lejeune VOCs, immunotoxicity, and bladder cancer etiology in their respective reports.<sup>3</sup> Their analyses were not sufficiently detailed to reliably support the opinions asserted. They fail to critically analyze the data and experimental studies concerning TCE, PCE, benzene, and vinyl chloride, with respect to their posited effects on the immune system and inflammatory responses. Again, studies that have explored whether Camp Lejeune VOCs have an effect on the immune system and inflammatory responses do not support plaintiffs' experts' opinions that VOCs can cause bladder cancer through immunomodulatory mechanisms.

---

<sup>2</sup> See General Causation expert report of Kathleen M. Gilbert, PHD on TCE, PCE, benzene and bladder cancer (dated December 9, 2024) ("Gilbert Bladder Cancer Report") at p. 20. Dr. Gilbert does not make arguments concerning the role of vinyl chloride, yet Dr. Laura M. Plunkett, Dr. Benjamin Hatten, Dr. Stephen H. Culp and Dr. Steven B. Bird all implicate vinyl chloride in the development of bladder cancer with superficial discussions of mechanism, if any. See Gilbert Bladder Cancer Report; Expert Report of Laura M. Plunkett, Ph.D., DABT (dated December 9, 2024) ("Plunkett Bladder Cancer Report"); Camp Lejeune: Bladder Cancer Expert Report of Benjamin Hatten, M.D., M.P.H. (dated December 9, 2024) ("Hatten Bladder Cancer Report"); Rule 26 Report of Stephen H. Culp, M.D., Ph.D. ("Culp Bladder Cancer Report"), General Causation Expert Report of Steven B. Bird, M.D. (dated December 9, 2024) ("Bird Bladder Cancer Report").

<sup>3</sup> Without elaboration, Dr. Plunkett and Dr. Bird implicate immunotoxicity and TCE, PCE, benzene *in addition to* vinyl chloride, the latter of which was not discussed in Dr. Gilbert's report. See Plunkett Bladder Cancer Report; Bird Bladder Cancer Report; see also Gilbert Bladder Cancer Report.

#### 4.0 QUALIFICATIONS

I, Michael J. McCabe, Jr., Ph.D., was retained by the United States to perform a thorough, independent and unbiased analysis concerning the toxicological issues in this case. I am an expert in the fields of toxicology, immunology, and related disciplines having earned a Ph.D. degree in Biomedical Studies in 1991 from Albany Medical College (New York) and having completed post-doctorate training from 1990 to 1992 in mechanistic toxicology at the Karolinska Institute (Stockholm, Sweden). My graduate education at Albany Medical College was through the Department of Microbiology and Immunology, which entailed didactic course work and qualifying examinations in immunology, microbiology, virology, cell and molecular biology, biochemistry, pharmacology, and toxicology. I trained in the laboratory of David A. Lawrence, Ph.D., who, in addition to running a first-rate research program focused on cellular immunology, operated the Albany Medical Center's clinical immunology laboratory. Also, in addition to my course work and thesis work, I moonlighted in various hospital laboratories (e.g., serology, bacteriology, blood bank), while at Albany Medical College.

After graduating and being awarded my Ph.D. degree, I was offered a post-doctoral position in the Institute of Environmental Medicine at the Karolinska Institutet under the mentorship of Sten Orrenius, M.D., Ph.D., who in addition to engaging in ground-breaking research concerning physiologic cell death (i.e., apoptosis), was a member of the Swedish Royal Academy of Sciences and Nobel Committee. Following my postdoctoral training period, I embarked on a career in academia. I have held academic appointments in the toxicology departments and environmental health science centers at Wayne State University (Detroit, Michigan) from 1992 to 2000 and the University of Rochester (Rochester, New York) from 2000 to 2017. At Wayne State, my academic responsibilities included serving as the Director of the Imaging and Cytometry Facility Core within the University's Environmental Health Science Center *Molecular and Cellular Toxicology with Human Applications*. Also, while on the faculty in the School of Medicine at the University of Rochester, I served as the Director of the Immunomodulators and Immunopathogenesis Research Core within the University's Environmental Health Science Center *Environmental Agents as Modulators of Human Disease and Dysfunction*. Currently, and since 2017, I have served as adjunct teaching faculty at Temple University (Philadelphia, Pennsylvania), where I teach a graduate level course in forensic toxicology.

I am an active 36-year member of the Society of Toxicology, which nationally and internationally is recognized as the premier scientific body dedicated to the purpose of advancing and promoting the field of toxicology. I am active in various sub-groups within the Society of Toxicology including the Immunotoxicology Specialty Section and the Ethical, Legal, Forensics and Societal Issues (ELFSI) Specialty Section. I have served on numerous



national and international advisory committees including for the National Institutes of Health (NIH), the National Academy of Sciences, the US Environmental Protection Agency (EPA), the Department of Defense and the World Health Organization (WHO). Also, I have sat on the editorial boards of four toxicology journals, including *Toxicology Letters* (2009-2013), *Journal of Immunotoxicology* (2004-2013), *Toxicology and Applied Pharmacology* (1999-2013), and *Toxicological Sciences* (2008-2015). As detailed on my CV, I have been widely published in peer-reviewed scientific journals and have received numerous research grants from the NIH both as Principal Investigator and as Co-Investigator.

In 2009, I left full-time employment in academia and embarked on a career in medico-legal consulting. Since 2009, I have been engaged hundreds of times to apply my expertise to assess the potential effects of chemical or biological exposures on human health. As a human disease causation expert, I often am called upon to apply fundamental principles of toxicology, immunology, and immunotoxicology in performing investigations and rendering opinions concerning potential adverse health effects associated with exposures to toxic substances. I have testified in forty-two matters at deposition, hearing or trial in the past four years. My current and complete *Curriculum Vitae* is appended to this report and includes a listing of my testimonies over the previous four years.

## **5.0 METHODOLOGY**

My opinions in this case were arrived at using the same methodology and scientific rigor that I have applied throughout my academic and consulting career performing research, authoring peer-reviewed manuscripts for publication, competing for and obtaining extramural funding for my research program, and assessing the scientific merit of ideas and works of other scientists through the peer review process. By and large, my approach involved testing hypotheses via the scientific method and consideration of attribution elements (e.g., Bradford Hill criteria) by relying on and searching the peer-reviewed scientific literature and other resources as well as my education, training, and experience.

My opinions and findings expressed in this report were derived from methodology that is generally accepted and relied upon by life scientists and toxicology experts. These opinions and findings are held to a reasonable degree of scientific certainty and are based on my extensive knowledge, education, training and experience in the fields of toxicology, immunology, cell biology, biochemistry, and related disciplines over the span of nearly forty years. As additional information becomes available, I may supplement or modify my opinions.

## 5.1 The Scientific Method and Bradford Hill Criteria

Plaintiffs' experts including Drs. Gilbert, Hatten, Plunkett, Culp and Bird have asserted that epidemiological studies support an association between bladder cancer and TCE, PCE, benzene, and vinyl chloride alone, or in combination with one another.<sup>4</sup> Other experts (e.g., Dr. Julie E. Goodman and Dr. Peter E. Shields) are rebutting those assertions. The "jumping in" place for me starts with addressing the question, "how can TCE, PCE, benzene, and vinyl chloride, alone or in combination with one another, cause bladder cancer"?

My work on this case is guided by the scientific method. The scientific method is a systematic approach used to conduct investigations in order to solve problems. The use of this method helps to ensure that scientific inquiry is objective, repeatable, and based on evidence.<sup>5</sup> My approach also considers what are known as Bradford Hill criteria (Hill, 1965), or modified Bradford Hill criteria (Adami et al., 2011; Fedak et al., 2015; Miller et al., 2000), which are a set of attribution elements that epidemiologists, toxicologists, and other scientists employ in performing a causation analysis. The nine attribution elements are strength of association, consistency, specificity, temporality, biological gradient, biological plausibility (i.e., mechanism or mode of action), coherence, experiment, and analogy. It is generally accepted that not all attribution elements must be met in order to establish causation. As indicated above, my work on this case focuses on the analysis and consideration of biological plausibility, by addressing whether perturbation of the immune system and inflammatory processes by TCE, PCE, benzene, and vinyl chloride, alone or in combination with one another, may be linked as valid mechanisms involved in the etiology of bladder cancer.

---

<sup>4</sup> Again, Dr. Gilbert does not make arguments concerning the role of vinyl chloride, yet Dr. Laura M. Plunkett, Dr. Benjamin Hatten, Dr. Stephen H. Culp and Dr. Steven B. Bird all implicate vinyl chloride in the development of bladder cancer with superficial discussions of mechanism, if any. See Gilbert Bladder Cancer Report; Plunkett Bladder Cancer Report; Hatten Bladder Cancer Report; Culp Bladder Cancer Report; Bird Bladder Cancer Report.

<sup>5</sup> The scientific method involves several key steps as follows: (1) Observation: Gathering background information or noticing something about a subject that prompts a question; (2) Hypothesis: Formulating a testable explanation or prediction based on the background information that has been collected; (3) Experimentation: Conducting experiments, gathering data or retrieving information to test the hypothesis; (4) Analysis: Examining the results of the experiments or retrieved information to determine whether the data support or contradict the hypothesis; (5) Conclusion: Drawing conclusions based on the analysis and deciding whether the hypothesis is supported or needs revision; (6) Replication: Repeating the experiment or study to verify results and ensure reliability; (7) Theory: If repeated testing confirms the hypothesis, it may become part of a broader scientific theory.

## **6.0 ANALYSIS AND BASIS OF OPINIONS**

My analysis and consideration of biological plausibility in this case (i.e., the mechanism(s) or mode(s) of action) that demonstrate how TCE, PCE, benzene, and vinyl chloride, alone or in combination with one another, could lead to the development of bladder cancer, if at all) involves the intersection of scientific principles related to toxicokinetics (the study of how the VOCs at issue are absorbed, distributed, metabolized, and excreted by the body), carcinogenesis (the study of cancer development), and immunology (the study of the human immune system, how it functions and responds to pathogens and other threats, and how it can become disordered).

In the sections that follow, I assess the toxicokinetics of PCE, TCE, benzene, and vinyl chloride, explain the importance of mechanisms of toxicity, and offer criticisms of the mechanistic opinions offered by plaintiffs' experts. I then discuss basic principles of carcinogenesis, provide an overview of the immune system, including immune responses such as immunosuppression, inflammation, and oxidative stress, and discuss the intricacies of the role that the immune system plays in both the prevention and promotion of bladder cancer. This information provides the conceptual framework necessary to address the opinions of Dr. Gilbert and other plaintiffs' experts concerning the alleged interconnections between TCE, PCE, benzene, and vinyl chloride, alone or in combination with one another, and their etiologic roles, if any, in the role of bladder cancer through immune/inflammatory mechanisms. My analysis continues with comprehensive discussions of peer-reviewed studies on TCE immunotoxicity in humans and animals, followed in turn by peer-reviewed studies concerning the immunotoxicity of PCE, benzene, and vinyl chloride in humans and animals. My analysis, as presented in these Sections, reveals that the current state of knowledge concerning TCE, PCE, benzene, and vinyl chloride immunotoxicity does not support the conclusion that immunomodulation (i.e., the process of changing the body's immune response) by these chemicals is operant in causing bladder cancer.

Having set out the conclusion of my analysis, I then outline criticisms of the opinions of plaintiffs' experts by pointing out deficiencies in the underpinnings of their opinions concerning mechanisms (i.e., modes of action, biological plausibility) of TCE-, PCE-, benzene-, or vinyl chloride-induced bladder cancer.

### **6.1 Volatile Organic Chemicals (VOCs) Identified at Camp Lejeune**

Volatile organic compounds (VOCs) are a group of carbon-containing chemicals that often are used as industrial solvents. VOCs have a high vapor pressure at room temperature—therefore, they can evaporate (i.e., volatilize) into air easily. Pathways of human exposure to VOCs include inhalation, as may more commonly occur with occupational exposures, or through ingestion or dermal contact. The VOCs at issue in the Camp Lejeune

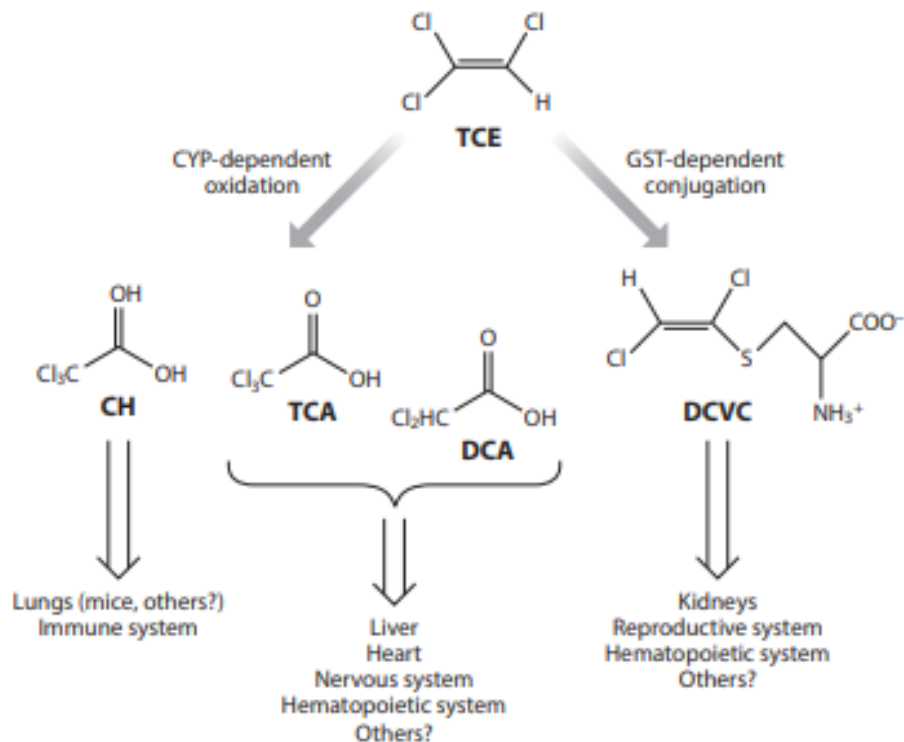
litigation are trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, and vinyl chloride (VC). The toxicokinetics of each of these chemicals in turn are discussed in the subsections that follow.

### **6.1.1 TCE Toxicokinetics**

TCE is a small, colorless, volatile liquid chemical that readily crosses cell membranes and is metabolized in the liver. Humans are exposed to TCE from a variety of sources and by different routes, including inhalation, ingestion, and dermal (ATSDR, 2019; USEPA, 2011). Regardless of the route of exposure, TCE readily crosses biological membranes, rapidly equilibrating from the circulation into richly perfused tissues including liver, kidney, and lung (Lash et al., 2000).

Although the metabolism of TCE is highly variable across sexes, species, tissues, and individuals, metabolism of TCE occurs through two separate pathways: (1) the oxidative metabolic pathway through cytochrome P450 (primarily CYP2E1), and (2) the glutathione (GSH) conjugation pathway (Lash, 2025; USEPA, 2011). In the oxidative pathway, metabolism yields chloral hydrate, trichloroacetate (TCA), and dichloroacetate (DCA). Although GSH conjugation of xenobiotics is often associated with detoxification, in the case of TCE, conjugation results in bioactivation through the formation of reactive and chemically unstable metabolite species (Lash, 2025; USEPA, 2011; ATSDR, 2019). Glutathione conjugation of TCE occurs primarily via glutathione-S-transferases (GSTs) in the liver, ultimately yielding S-dichlorovinyl-L-cysteine (DCVC). Both metabolic pathways are summarized in Figure 1. After metabolism, TCE is excreted either unchanged in expired air or as metabolites in the urine (ATSDR, 2019). Excretion of TCE in the bile apparently represents a minor pathway of elimination.

**Figure 1. Metabolism of TCE (Lash, 2025).**



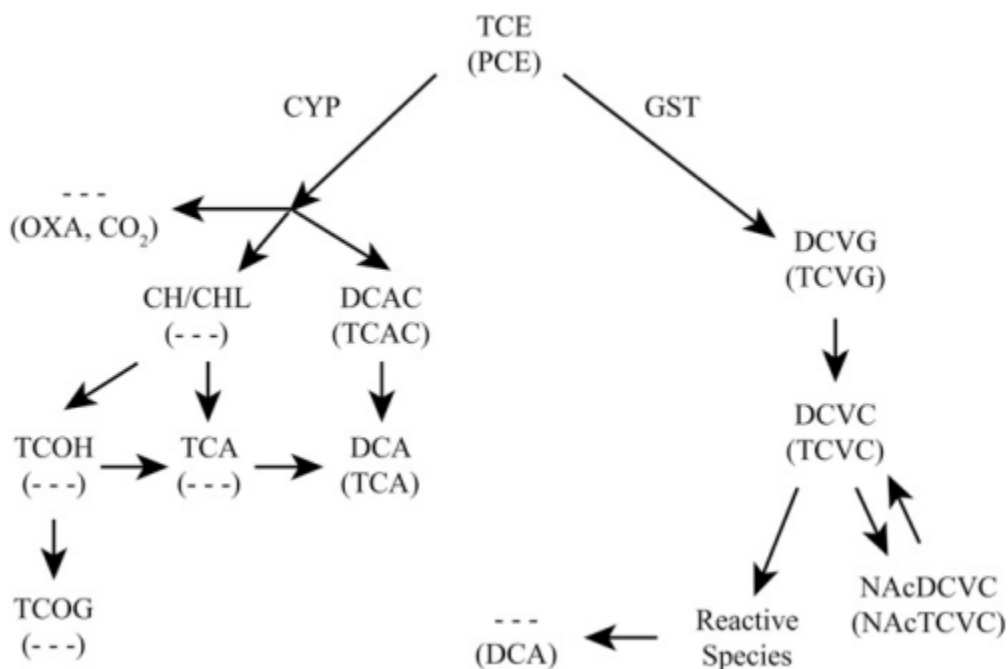
### 6.1.2 PCE Toxicokinetics

Perchloroethylene (also known as tetrachlorethylene, PERC, or PCE) is a colorless liquid at room temperature and highly lipophilic PCE is known for its use in the dry-cleaning industry as a degreasing solvent and as a chemical synthesis intermediate. (ATSDR, 2019b). PCE is readily absorbed following inhalation (primary route), oral, and minimally by direct dermal exposure (ATSDR, 2019b). In both animal studies and human cases of accidental death, absorbed PCE is distributed throughout the body regardless of the route of exposure, with highest concentrations measured in the adipose tissue, liver, and kidney (Dallas et al. 1994a, 1994b; Levine et al., 1981; Lukaszewski, 1979; Pegg et al., 1979; Savolainen et al., 1977).

PCE is metabolized through similar metabolic pathways as TCE: (1) through oxidation by cytochrome P-450 isozymes and (2) glutathione conjugation via glutathione-S-transferase (Fig. 2). While pathways are similar in humans and rodents, the predominant pathway varies by species and exposure route, with evidence for dose-dependency as well (Lash, 2025; Cichocki et al., 2016; ATSDR, 2019b). In humans, regardless of the route of exposure, only 1–3% of the absorbed PCE is metabolized to trichloroacetic acid. Of note, mice and rats metabolize more PCE to trichloroacetic acid (144 and 710 nmol/minute/kg) compared to humans (13 nmol/minute/kg).

Oxidative metabolism of PCE occurs in the liver, lung, and kidney, and is mediated by CYP2E1, based on data for similar compounds, but other isozymes may also be involved (Chiu and Ginsberg, 2011; Lash and Parker, 2001). Oxidation is believed to yield an Fe-O intermediate, which is converted to trichloroacetyl chloride and then hydrolyzed to trichloroacetic acid (Chiu and Ginsberg 2011). An epoxide intermediate, initially believed to be the progenitor to trichloroacetic acid, was shown to decompose to ethanedioyl dichloride and then to CO and CO<sub>2</sub>; this pathway is believed to be minor (Chiu and Ginsberg 2011). Oxalic acid is also a metabolite of PCE oxidation and may occur via either the epoxide or Fe-O intermediate (ATSDR, 2019b). The urinary metabolites of PCE are trichloroacetic acid and dichloroacetic acid (DCA) and are the proximate toxicants responsible for the liver toxicity and carcinogenicity seen in PCE-exposed mice (Buben and O'Flaherty 1985; Chiu and Ginsberg 2011; Lash and Parker 2001). However, DCA is formed in the kidney in rodents through the GSH conjugation pathway (instead of through oxidative metabolism as occurs with TCE). This pathway leading to formation of the DCA metabolite has not been demonstrated in humans. Glutathione conjugation of PCE occurs primarily in the liver and kidney, producing trichlorovinyl glutathione and then S-trichlorovinyl-L-cysteine (TCVC) (Chiu and Ginsberg, 2011; Lash and Parker, 2001). TCVC can then be metabolized to reactive species via beta-lyase or flavin-containing monooxygenases (FMOs) (Anders et al., 1988; Krause et al., 2003). Of note, a study by Seiji et al. (1990) showed that in workers exposed to TCE and PCE, the metabolism of TCE was suppressed by co-exposure to PCE.

**Figure 2. Metabolism of PCE. (Cichocki et al., 2016)**



Regardless of the route of exposure, most (>80%) of the absorbed dose of PCE is exhaled unchanged in humans (ATSDR, 2019b). The major urinary metabolite in humans is trichloroacetic acid, which is at a 100-fold higher concentration than the second major urinary metabolite, NAcTCVC (Volkel et al. 1998). No dichloroacetic acid was detected in human urine. The elimination half-life in humans was 45.6 hours for trichloroacetic acid and 14.1 hours for NAcTCVC (Birner et al. 1996).

### **6.1.3 Benzene Toxicokinetics**

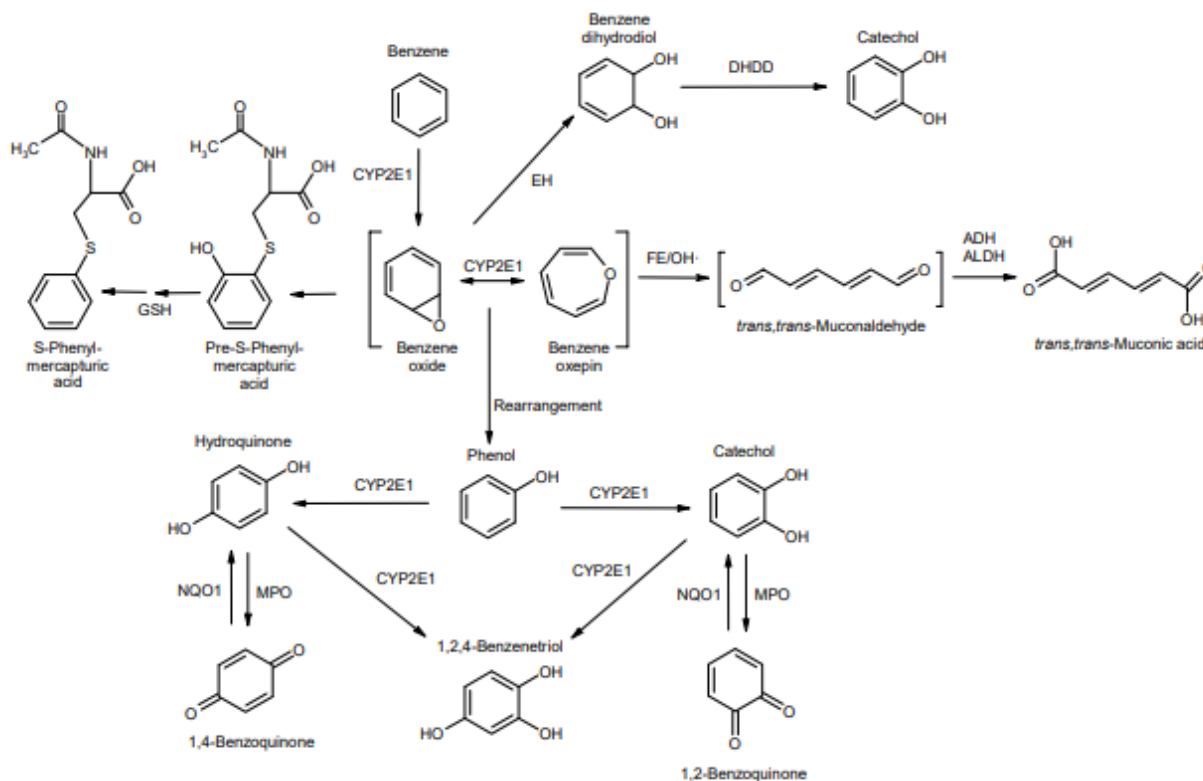
Benzene is an aromatic hydrocarbon and comes mostly from anthropogenic sources, including combustion (ATSDR, 2024b). It is ubiquitous in the environment as part of gasoline, vehicle exhaust, industrial emissions, and tobacco smoke, and has been used as a solvent in industry and consumer products.

Benzene is readily absorbed via inhalation, oral, and dermal routes in both animals and humans (ATSDR, 2024b). Inhalation exposure is the major route of human exposure to benzene; at concentrations between 47 and 110 ppm, absorption is highest in the first few minutes of exposure (70–80%) but decreases by about 1 hour to approximately 50% (range, 20–60%) with considerable individual variability (Srbova et al. 1950). Since benzene is lipophilic (tending to combine with or dissolve in lipids or fats), it is distributed throughout the body following absorption into blood and distribution to fatty tissue as expected.

Benzene is metabolized by cytochrome P450 2E1 (CYP2E1), forming an epoxide, benzene oxide. Benzene oxide may then proceed through several alternative metabolic pathways (Jerina et al., 1968; Lovern et al., 1997). In one pathway, benzene oxide rearranges nonenzymatically to form phenol, the major product of initial benzene metabolism. Phenol is further oxidized by CYP2E1 to hydroquinone. Further oxidation of hydroquinone to p-benzoquinone is catalyzed by myeloperoxidase (MPO). In a second pathway, benzene oxide can also react with glutathione (GSH) to form phenylmercapturic acid and thereafter be converted by epoxide hydrolase to benzene dihydrodiol with subsequent formation of catechol. In a third pathway, an iron-catalyzed ring-opening reaction results in the formation of trans,trans-muconaldehyde (MUC) with further metabolism to trans,trans-muconic acid (MA). All of the phenolic products may be conjugated with sulfate or glucuronic acid, with the conjugates of phenol and hydroquinone, the major benzene metabolites, excreted in urine (Sabourin et al., 1989; Wells and Nerland, 1991). Benzene metabolism also occurs in the bone marrow and other tissues.

Benzene is excreted both unchanged via the lungs and as metabolites (but also as parent compound in small amounts) in the urine. The rate and percentage of excretion via the lungs are dependent on exposure dose and route. Qualitatively, the metabolism and elimination of benzene appear to be similar in humans and laboratory animals (Henderson et al., 1989; 1996; Sabourin et al., 1988).

**Figure 3. Metabolism of Benzene<sup>7</sup>.**



### 6.1.4 Vinyl Chloride Toxicokinetics

Vinyl chloride (VC) is a volatile compound used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC). VC is rapidly and efficiently absorbed via the inhalation and oral routes and is rapidly converted to water-soluble metabolites in both animals and humans (ATSDR, 2024).

In rats, metabolic pathways for VC are consistent for both inhalation and oral exposure, with the primary route of metabolism through cytochrome P450 2E1 to form

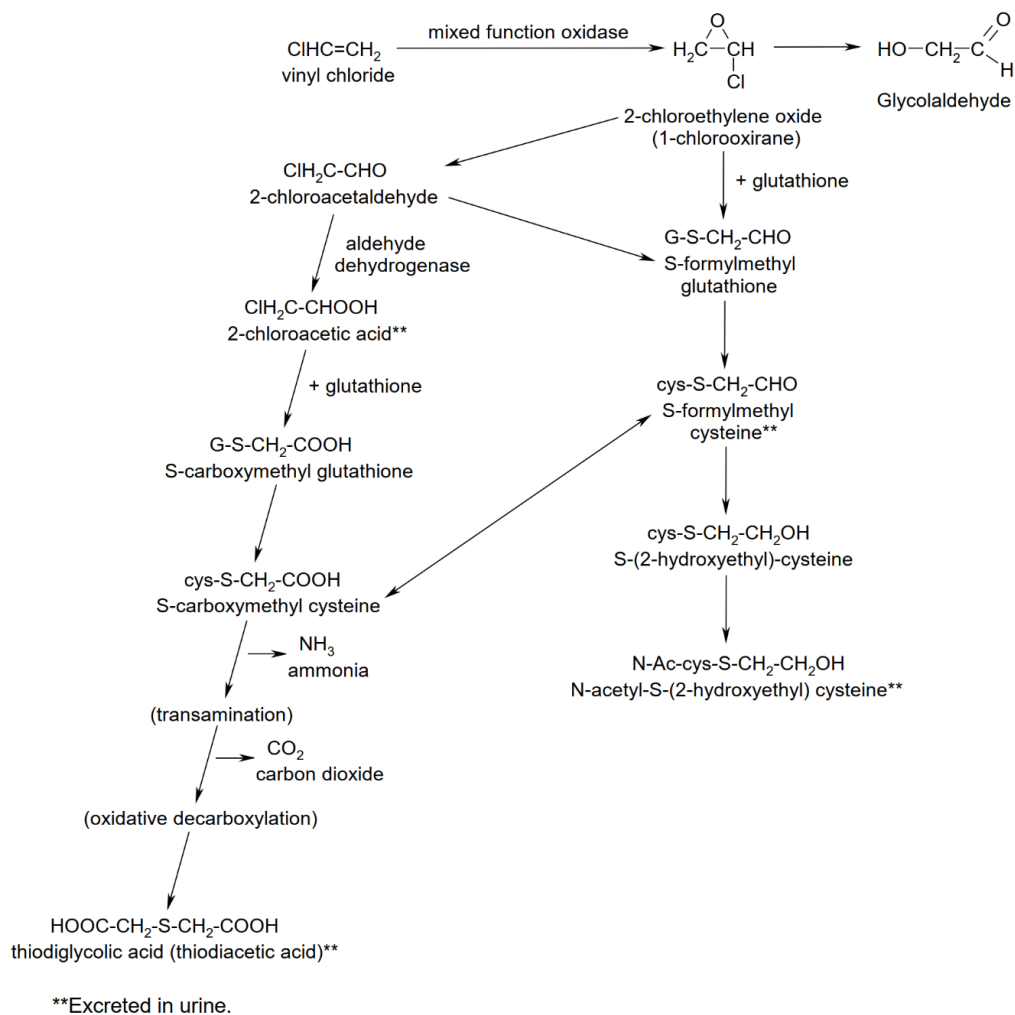
<sup>7</sup> Key: ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; CYP2E1 = cytochrome P450 2E1; DHDD = dihydrodiol dehydrogenase; EH = epoxide hydrolase; GSH = glutathione; MPO = myeloperoxidase; NQO1 = NAD(P)H:quinone oxidoreductase (from ATSDR, 2024).



chloroethylene oxide (ATSDR, 2024). CYP2B1 plays a role in VC metabolism in rodents (Ivanetich et al., 1977). Chloroethylene oxide (CEO) is a highly reactive, short-lived epoxide that rapidly rearranges to form chloroacetaldehyde (CAA), a reactive halocarbonyl compound; CEO is also a substrate for epoxide hydrolase (Pessayre et al., 1979). Both of these metabolites are detoxified primarily via glutathione (GSH) conjugation catalyzed by glutathione S-transferase (Jedrychowski et al., 1985; Leibman, 1977; Tarkowski et al., 1980). CEO can also be detoxified by epoxide hydrolase to yield glycolaldehyde. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) may also play a role in detoxifying CEO (Chen et al., 2019). A simplified diagram of the metabolism of VC is shown in Figure 4.

At low concentrations, VC metabolites are rapidly excreted primarily in urine, while at high exposure concentrations, unchanged VC is also eliminated in exhaled air (ATSDR, 2024). Urinary metabolites in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al., 1975b; Watanabe et al., 1976b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al., 1975b). CAA and CEO GSH conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-formylmethylcysteine, and N-acetyl-S-(2-hydroxyethyl) cysteine (Bolt et al., 1980; Hefner et al., 1975b).

**Figure 4. Metabolism of Vinyl Chloride.**



### 6.1.5 Genotoxic and Non-genotoxic Agents

Chemicals are often divided into two categories based on whether their general mode of action is genotoxic or non-genotoxic. Genotoxic agents interact with DNA, resulting in damage or structural change, and are typically mutagenic in a dose-responsive manner (Klaassen, 2019). These DNA-reactive agents can be further subdivided according to whether they can directly bind to DNA without being metabolized (direct-acting) and those that require biotransformation to bind DNA (indirect-acting). Most chemical agents that function at the initiation stage of the cancer process are indirect-acting genotoxic compounds that require metabolic activation in the target cell to result in DNA damage. The plaintiffs' experts' proposed genotoxic mechanisms are addressed in Section 6.2, Mechanisms of VOC Toxicity.

Non-genotoxic agents do not directly interact with nuclear DNA but may change gene expression, modify normal cell function, bind to or modify cellular receptors, and increase cell growth (Klaassen, 2019). Non-genotoxic agents function through epigenetic mechanisms, changing DNA expression without modifying or directly damaging its structure. Non-genotoxic chemicals can make a cell or tissue more susceptible to DNA damage from other natural or xenobiotic (i.e., foreign chemical) sources. The plaintiffs' experts' proposed non-genotoxic mechanisms for immune system modulation are addressed in Section 6.6, Immunotoxicity.

## 6.2 Mechanisms of VOC Toxicity

The toxicity of a chemical is determined by its toxicokinetics, the factors discussed above (i.e., a chemical's structure and how it is absorbed, distributed, metabolized, and excreted or detoxified by the body). Much is known about the metabolism of TCE, PCE, benzene, and vinyl chloride and the importance of different metabolic pathways and formation of different reactive metabolites in the potential mechanisms of their toxicities. Metabolism of TCE, PCE, benzene, and vinyl chloride can result in both intoxication and detoxification, meaning that the chemicals are metabolized in the body in ways that can sometimes have harmful effects or in ways that transform them into compounds that can be easily excreted from the body.

The metabolites produced when these chemicals are broken down in the body are often target-organ specific. For example, as shown in Figure 1, different modes of action and target-organs specific effects of TCE have been found with various TCE metabolites (Lash, 2025). As described earlier, metabolism of TCE occurs through two separate pathways: (1) the oxidative metabolic pathway, and (2) the GSH conjugative pathway. The oxidative pathway that begins with the cytochrome P450 (CYP)-dependent oxidation of TCE to chloral hydrate (CH) is associated with immune system effects, while the oxidative metabolites TCA (trichloroacetate) and DCA (dichloroacetate) mediate effects on the liver, heart, nervous system, hematopoietic system, and possibly other tissues. The GSH conjugative pathway starts with a conjugation reaction between TCE and glutathione (GSH) catalyzed by the enzyme glutathione-S-transferase (GST) to form cysteine-S-conjugate S-(1,2-dichlorovinyl)-L-cysteine (DCVC). The DCVC metabolite is associated with toxicity for the kidney, reproductive system, hematopoietic system, and possibly others. Thus, different metabolites are produced depending on the metabolic pathway, and those various metabolites are target-organ specific, meaning that a metabolite that is formed in the liver may have no effect on a different organ or tissue, such as the bladder.

Although metabolism of certain VOCs is somewhat similar, there are also important differences, including the particular metabolites and quantify of potentially reactive metabolites produced. For example, PCE and TCE metabolism are qualitatively similar, but quantitative differences in the flux and yield of metabolites exist. For example, like TCE, the oxidative metabolism of PCE is believed to be carried out by CYP2E1, but the formation of the CH and DCA metabolites is more prominent with TCE. In PCE-exposed rodents, DCA is formed in the kidney, not through oxidative metabolism, but through the GSH conjugation pathway; however, this source of DCA attributable to PCE exposure has not been demonstrated in humans. Also, like TCE, GSH conjugation of PCE catalyzed by GST occurs in the liver and kidney with DCVC and TCVC being the precursors for reactive metabolites produced for TCE and PCE, respectively. Of note, in humans and experimental animals, the total metabolic flux through oxidation has been shown to greatly exceed GSH conjugation, which means that the quantity of the respective metabolites that are produced through both pathways are not equivalent. Therefore, there are significant differences between the quantity of various metabolites produced for both TCE and PCE that impact their toxicities—they are not the same. These differences are significant when analyzing the dose-dependent effects of VOCs on the immune system and other organs and tissues.

Humans are exposed to potentially harmful substances on a daily basis, but those exposures do not necessarily lead to disease. There are complex interactions between intrinsic factors (e.g., genes) and extrinsic factors (e.g., environmental) that ultimately determine whether an adverse biological response occurs. As an example, the reactive metabolites derived from the glutathione conjugation pathway of TCE and PCE have been shown to elicit downstream biochemical reactions as well as cellular disruptions such as mitochondrial dysfunction and oxidative stress, and a myriad of other effects that have been shown in animal *in vivo* and *in vitro* studies to be capable of causing genotoxic and non-genotoxic outcomes. These findings provide a conceptual framework supporting the plausibility that such adverse toxic effects could be operant mechanistically in the carcinogenic process, generally. However, the manifestation of these toxic effects depends on numerous variables including exposure dose and duration, the triggering of detoxifying mechanisms (e.g., antioxidant enzymes, DNA repair mechanisms), and a person's physiological characteristics such as age, gender, and genetic polymorphisms (i.e., the different genetic makeup of each person).<sup>8</sup>

---

<sup>8</sup> Interestingly, GST polymorphisms in humans may play a role in interindividual variability in susceptibility to the toxicity of TCE and PCE (Cichocki et al., 2019; Lash et al., 2014; Moore et al., 2010). This is a specific example of the complex interactions that occur between intrinsic and extrinsic factors that are the focus of contemporary environmental medicine research. Understanding these specific gene-to-environment interactions are key to our improved understanding of the etiologies of many idiopathic chronic diseases.

### **6.2.1 Criticisms of Proposed Mechanisms of VOC Toxicity**

The importance of these details above are, by and large, dismissed, ignored, or glossed over by plaintiffs' experts. Individually and collectively, plaintiffs' experts take the position that all exposures to TCE, PCE, benzene, and vinyl chloride, in all combinations, produce harmful toxic effects that can contribute to bladder cancer (as well as a host of other cancer and non-cancer diseases) through the same vaguely described mechanisms. Each expert seemingly takes an approach that amounts to "checking the box" with respect to Biological Plausibility as a Bradford Hill attribution element.

#### **6.2.1.1 Dr. Gilbert's Proposed Mechanisms**

For example, Dr. Gilbert acknowledges that the ability of TCE, PCE, and benzene-induced genotoxicity to cause bladder cancer has not been studied.<sup>9</sup> Nevertheless, she proceeds to offer the novel, but weak, argument that, since TCE (but not PCE or benzene) genotoxicity has been demonstrated in the kidney, "some" unquantified and unidentified TCE metabolite(s) could travel from the kidney to the bladder where they produce heretofore unreported genotoxic events, thereby initiating bladder cancer.<sup>10</sup> Moreover, Dr. Gilbert did not reconcile how PCE or benzene might produce genotoxicity relevant to bladder cancer given the acknowledged absence of any experimental studies or data demonstrating that genotoxicity relevant to bladder cancer occurs. It must be emphasized that such vagaries and leaps in logic demonstrate the flawed premise on which Dr. Gilbert's analysis and resulting opinions are built.

#### **6.2.1.2 Dr. Bird's Proposed Mechanisms**

Dr. Steven Bird indicates that the mechanism of action for PCE and bladder cancer generally involves i) metabolic activation, ii) genotoxicity, iii) oxidative stress, and iv) cellular and molecular pathways.<sup>11</sup> Dr. Bird's general premise appears to be that PCE metabolites cause mutations either directly (e.g., reactive metabolites) or indirectly (e.g., reactive oxygen species). These mutations then disrupt cellular and molecular pathways involved in cell division and/or cell death. Missing is any coherent discussion from Dr. Bird concerning

---

<sup>9</sup> Dr. Gilbert acknowledged that the roles of TCE-, PCE-, and benzene-induced genotoxicity in causing bladder cancer specifically has not been studied. Gilbert Bladder Cancer Report, p. 15. She elaborated that *"it is possible that some"* genotoxic reactive metabolites of TCE, PCE or benzene produced in the kidney could travel to the bladder; however, she did not quantify the DNA damage she inferred would occur. Gilbert Bladder Cancer Report, p. 16.

<sup>10</sup> Gilbert Bladder Cancer Report, p. 15.

<sup>11</sup> Gilbert Bladder Cancer Report, p. 17-19.

details necessary to support an opinion relevant to this case. These details include: 1) dose and duration of PCE exposure required to provoke these mechanisms, 2) specific PCE metabolites involved, and 3) effects of PCE at doses relevant to water at Camp Lejeune on specific genes associated with cellular and molecular pathways tied to bladder carcinogenesis. As the basis of his opinion that these mechanisms are involved in PCE-induced bladder cancer, Dr. Bird cites an article by Cichocki et al. (2016). However, the Cichocki study contradicts Dr. Bird's conclusion, stating that "[n]o evidence for urinary bladder carcinogenesis was observed in studies in experimental animals for PCE (or TCE), and there is currently no mechanistic evidence to provide biologic plausibility in support of a hypothesis of PCE-associated bladder cancer."<sup>12</sup> Thus, Dr. Bird has provided no evidence for his assertion.

Dr. Bird indicates that the mechanism of action for TCE and bladder cancer generally involves i) DNA damage and mutagenicity, ii) epigenetic modifications, iii) selective growth advantage, iv) inhibition of apoptosis, and v) oxidative stress and inflammation. Dr. Bird provides few, if any, details or direct experimental evidence that these mechanisms are operant in TCE causing bladder cancer. His list of postulated mechanisms tracks with hallmarks of carcinogenesis that one might hypothesize could be affected by any environmental agent in any cancer. Indeed, Dr Bird follows the discussion of PCE and TCE by implicating benzene and vinyl chloride in causing bladder cancer by similar mechanisms, all under the guise of satisfying Bradford Hill criteria for biological plausibility.

As the basis of his opinion that epigenetic modifications are involved in TCE-induced bladder cancer, Dr. Bird cites an article by Rusyn et al. (2014). However, the Rusyn study states only that "...these data support the plausibility of a hypothesis that dysregulation of gene methylation may play a role in TCE-induced tumorigenesis," and "no data from humans or experimental animals are available specifically testing this hypothesis for TCE."<sup>13</sup> Thus, the Rusyn study only proposes an untested hypothesis; it does not provide evidence for Dr. Bird's assertion.

#### **6.2.1.3 Dr. Plunkett's Proposed Mechanisms**

Dr. Plunkett opines that the Biological Plausibility attribution element of Bradford Hill is satisfied by virtue of there being sufficient evidence showing that PCE, TCE, and benzene are involved in carcinogenesis because, stepwise, exposure to these chemicals results in the formation of reactive metabolites in the liver and kidney (step one), these reactive metabolites are excreted into urine (step 2), where they come into contact with the urothelial

---

<sup>12</sup> Page 115, Cichocki et al., 2016.

<sup>13</sup> Page 60, Rusyn et al., 2014.

cells in the bladder, (step 3). Thus, Dr. Plunkett infers that exposure to these chemicals can causes genotoxic events that lead to bladder cancer. Dr. Plunkett's opinion is based only on generalities. Dr. Plunkett provides few, if any, details or direct experimental evidence that these mechanisms are actually operant in causing bladder cancer.<sup>14</sup>

#### **6.2.1.4 Dr. Hatten's Proposed Mechanisms**

Dr. Hatten's take on Biological Plausibility is similar to Dr. Plunkett's that each of the VOCs can cause bladder cancer because (1) reactive metabolites for each chemical are formed in the kidney, (2) although there is no direct evidence of an effect in the bladder, these reactive metabolites could travel from the kidney to the bladder, and (3) the activities of these reactive metabolites in the urothelium must be operant in causing bladder cancer because, according to plaintiffs' experts, there is some evidence that each chemical causes bladder cancer. This is circular reasoning with no evidentiary support, only speculation. Dr. Hatten acknowledges that causal mechanisms connecting benzene and vinyl chloride exposures to bladder cancer have not been investigated. Nevertheless, despite the lack of information, Dr. Hatten opines that there are plausible mechanistic connections.<sup>15</sup>

More specifically, Dr. Hatten opines that there are biologically plausible mechanistic pathways for TCE, PCE, benzene and vinyl chloride to cause bladder cancer. However, in this regard, Dr. Hatten does not appear to understand the difference between a plausible hypothesis concerning mechanism of action for chemical carcinogenesis and experimental evidence demonstrating that it is so. Dr. Hatten's opinion regarding the mechanism by which TCE causes bladder cancer by and large centers on the glutathione conjugation pathway of TCE metabolism that has been implicated in bladder toxicity.<sup>16</sup> Per Dr. Hatten, the mechanism by which PCE causes bladder cancer follows that of TCE (i.e., glutathione conjugation), because as Dr. Hatten points out the metabolism of PCE and TCE are similar<sup>17</sup>, which is true qualitatively but not quantitatively. Dr. Hatten provides no critical assessment concerning differences between TCE and PCE metabolism, formation of reactive metabolites, and differences in outcomes concerning toxicity between the two compounds. These known differences undermine Dr. Hatten's conclusion that the biologically plausible mechanism for TCE and PCE are the same. Dr. Hatten acknowledges that *"...the literature base is too limited to define a precise pathway or mechanism of injury for vinyl chloride exposure leading to the*

---

<sup>14</sup> Plunkett Bladder Cancer Report, p. 49.

<sup>15</sup> Hatten Bladder Cancer Report, p. 19-20, 25, 30, 32.

<sup>16</sup> Hatten Bladder Cancer Report, p. 23.

<sup>17</sup> Hatten Bladder Cancer Report, p. 39.

*development of bladder cancer*<sup>18</sup>, but he infers that the mechanism of vinyl chloride causing bladder cancer could involve activation of the RAS and p53 oncogenes.<sup>19</sup> However, Dr. Hatten fails to point out that vinyl chloride-induced RAS mutations are species and cell type dependent (i.e., they have been found in rat liver tumors induced by vinyl chloride) (Boivin-Angele et al., 2000). Mutations in p53 also have been associated with liver tumors in humans and rodents exposed to vinyl chloride (ATSDR, 2019). I am not aware of any studies demonstrating vinyl chloride-induced mutations in p53 or RAS that have been implicated mechanistically in bladder cancer—and Dr. Hatten did not cite any studies to that effect. With respect to benzene, Dr. Hatten acknowledges<sup>20</sup> that *“...research is too limited to define a precise pathway or mechanism of injury for vinyl chloride exposure leading to the development of bladder cancer”* (page 39). “Nevertheless, despite the lack of information, Dr. Hatten opines that it is reasonable to conclude that a biologically plausible mechanism of action exists that links benzene exposure to bladder cancer. Finally, Dr. Hatten states that *“...the absence of well-developed mechanistic and animal models does not imply lack of causation.”*<sup>21</sup> Although I don’t agree with that statement, it certainly is true that failing to critically evaluate the existing mechanistic data does not aid in establishing causation.

As mentioned above, plaintiffs’ experts, particularly Dr. Gilbert, implicate immunotoxicity associated with Camp Lejeune VOCs as a plausible mechanism involved in the etiology of bladder cancer. Except for Dr. Gilbert, none of the other plaintiffs’ experts are immunologists. My opinion is that experimental studies and data do not support that modulation of the immune system is a plausible mechanism by which TCE, PCE, benzene, and vinyl chloride can cause bladder cancer.

In the Sections that follow, I present basic principles of carcinogenesis, provide an overview of the immune system, including immune responses such as immunosuppression, inflammation, and oxidative stress, and discuss the intricacies of the role that the immune system plays in both the prevention and promotion of bladder cancer. This information provides the conceptual framework necessary to follow my ensuing analysis and understand my opinion as well as the flaws in the opinions of Dr. Gilbert and other plaintiffs’ experts concerning the alleged interconnections between TCE, PCE, benzene, vinyl chloride, alone or

---

<sup>18</sup> Hatten Bladder Cancer Report, p. 40.

<sup>19</sup> Hatten Bladder Cancer Report, p. 35.

<sup>20</sup> Hatten Bladder Cancer Report, p. 39.

<sup>21</sup> Hatten Bladder Cancer Report, p. 5.



in combination with one another, and their etiologic roles, if any, in the role of bladder cancer through immune/inflammatory mechanisms.

## **6.3 Overview of the Immune System**

Overall, the immune system is a complex network of cells (e.g., lymphocytes, macrophages, neutrophils, dendritic cells, etc.) and soluble mediators (e.g., antibodies, cytokines, complement proteins, etc.) within the body that function to protect against infections such as viral or bacterial pathogens or other threats to the integrity of oneself, while simultaneously preserving the functioning of the body's own cells, tissues and organs. (Parham, 2015). In this way, the immune system essentially functions as the body's "Department of Defense," being charged with defending the integrity of self and protecting the body from harm by identifying (i.e., recognizing) threats and eliminating them before they can cause too much harm. The immune system achieves this through a combination of so-called innate immune and adaptive immune responses.

### ***6.3.1 Innate and Adaptive Immunity***

#### ***6.3.1.1 Innate Immunity***

**Innate immunity** is the body's first line of defense against invading pathogens and responds more quickly upon the body's first encounter with a pathogen.<sup>22</sup> Innate immunity also referred to as natural immunity because the mechanisms affording protection are conserved evolutionarily and present at birth. Generally, innate immunity is more primitive than adaptive immunity, and antigenic recognition by cells of the innate immune system is non-specific and involves less diversity. Innate immunity is comprised of physical barriers such as the skin and mucous membranes, as well as various cell types including phagocytes (i.e., white blood cells) such as macrophages and dendritic cells. Innate immunity also is comprised of other white blood cells (i.e., leukocytes) that have specialized functions including mast cells, basophils, eosinophils, neutrophils and natural killer cells. Natural killer cells (NK cells) play a particularly important role in the body's defense against viruses and cancer.

#### ***6.3.1.2 Adaptive Immunity***

Adaptive immune responses, or **adaptive immunity**, involve the development of immunological memory, that is, the ability of the immune system to recognize and respond more effectively to pathogens or antigens that have been encountered previously. Features of immunological memory include quicker onset and amplification of the immune response

---

<sup>22</sup> The components of a pathogen or other perceived foreign entity to which the immune system responds are called **antigens**. More broadly, an antigen is anything in the body that the immune system perceives as not belonging and attempts to fight.

upon re-encounter with pathogens. These features of immunological memory are fundamental to the success and efficacy of vaccine immunization programs.

Vaccines, which typically are biological preparations containing antigenic components of pathogens or killed or attenuated pathogen variants, activate the adaptive immune response, thereby creating immunological memory that confers long-lasting protective immunity specific to the vaccine target pathogen. The benefit of vaccination is that, upon subsequent encounter with the vaccine target pathogen, the attack by the immune system is more robust, thereby protecting the host from the harmful effects of infection.<sup>23</sup>

Memory immunity is not just important for vaccines; it is a feature of many secondary immune responses (i.e., immune responses that occur subsequent to a host's first-time encounter with an antigen). Therefore, adaptive immunity entails the response of antigen-specific B lymphocytes and T lymphocytes to antigen. Antigen-specific B lymphocytes differentiate into plasma cells, which secrete antibodies that bind to pathogens or antigens (i.e., **immune recognition**)<sup>24</sup> and facilitate their destruction and/or removal through **immune effector** processes that include neutralization, opsonization or death of antigen-expressing cells (i.e., cytotoxicity).

#### **6.3.1.2.1 T CELL SUBPOPULATIONS**

In adaptive immunity, there are many subpopulations of antigen-specific T lymphocytes (Fig. 5). Functionally distinct T lymphocytes express different arrays of receptors (e.g., different combinations of CD4, CD8, CD25 and CD45RA—all of which are designations for cell surface markers on T cells) on their cell surfaces, which impart specialized roles for the T cell subtype during an immune response.

CD4+ cells, also called T helper cells, function by regulating the activities of other immunocytes and “helping” them to perform their roles such as, for example, B cells differentiating into antibody-secreting plasma cells.<sup>25</sup> There are various subpopulations of

---

<sup>23</sup> For example, although polio and measles are both extrinsic pathogenic viruses, when a host is infected solely with measles virus, the immune response is targeted specifically to activate against measles, and not polio (or any of the other incalculable number of pathogens or antigenic threats that could be encountered by the host in other circumstances).

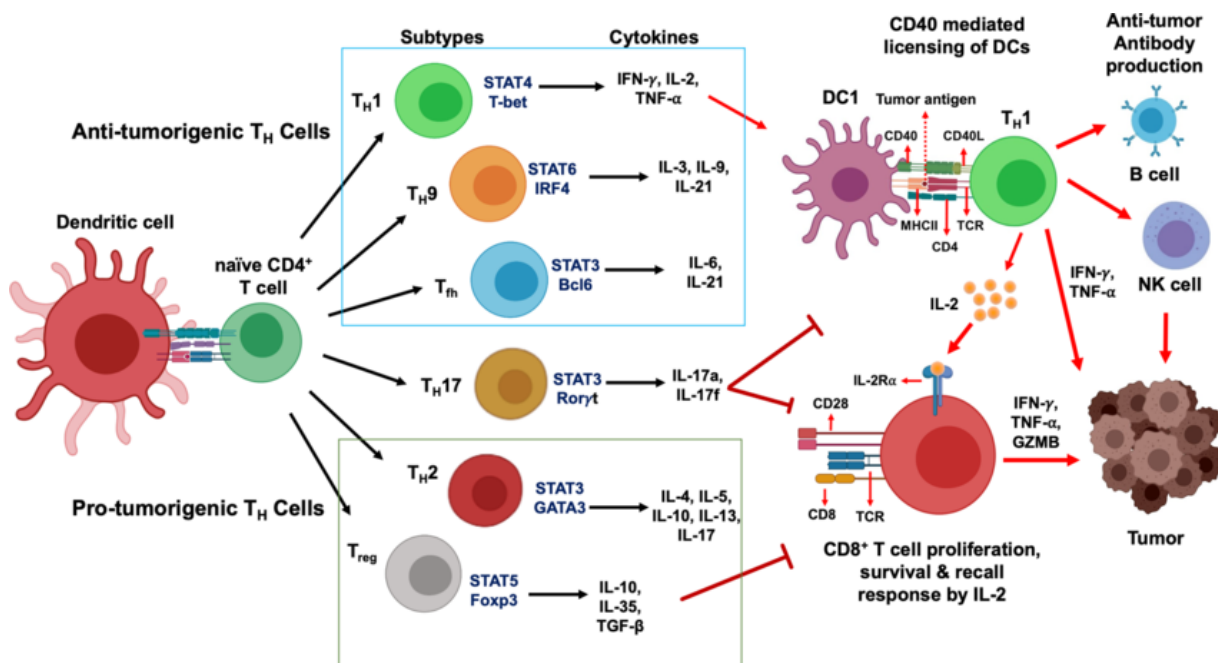
<sup>24</sup> **Immune recognition** is the process by which certain specialized cells of the immune system identify specific antigens thereby distinguishing between self and non-self. Immunology: The Science of Self-Nonself Discrimination. John Wiley & Sons. The concepts of specificity and self-nonsel self discrimination are fundamental tenets of immunology.

<sup>25</sup> The critical importance of CD4+ cells in immunity is exemplified by Acquired Immunodeficiency

CD4+ helper T cells, which are functionally distinct and control different aspects of the immune response based on the cytokines that they produce (Basu et al., 2021; Geginat et al., 2014; Kunzli & Masopust., 2023). For example, CD4+ Th1 cells produce interleukin-2 (IL-2), tumor necrosis factor (TNF- $\alpha$ ), and interferon gamma (IFN- $\gamma$ ); whereas, CD4+ Th2 cells produce interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10), and interleukin-13 (IL-13). The effector functions of Th1 and Th2 cells differ, in that, Th1 cells tend to aid cell-mediated immune responses (e.g., CD8+ CTL responses); whereas Th2 cells tend to aid humoral immune responses (e.g., antibody production by B cells).

Another subpopulation of CD4+ cells is called Tregs (i.e., Regulatory T cells) that function normally to suppress (i.e., turn-off) immune responses through a variety of mechanisms including secretion of IL-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ). Changes in the activities of Tregs is associated with many chronic diseases including allergies, autoimmune diseases and cancer. The following figure illustrates the complex central role that CD4+ T cell differentiation and different CD4+ T cell subsets play in immunity.

**Figure 5. CD4+ T Cells Development and Their Functional Subsets in Immunity (Basu et al., 2021).**



Syndrome (AIDS), where infection with the Human Immunodeficiency Virus (HIV) is characterized by massive reduction of CD4+ T cells. Consequently, left untreated, HIV infection leads to severe immunodeficiency followed by death and morbidity due to opportunistic infections and certain malignancies that develop secondary to impaired immune responses to infectious agents.

CD8+ cytotoxic T lymphocytes (CTLs) also play a major role in the body's adaptive immune defenses and ability to fight viral infections. When certain viruses infect cells, they express proteins or otherwise cause cell surface changes that can be recognized by CTLs as being "foreign." Recognition of the virus-infected cells by CTLs then triggers a targeted effector function whereby the CTL delivers a "hit" in the form of a cytotoxic granule containing the protein perforin to the virus infected cell.

## **6.4 Role of the Immune System in Cancer Development**

By and large, the mechanisms the immune system employs to fight infections with pathogens are the same, or similar, as those directed toward controlling the growth of a cancerous tumor.

The immune system can combat cancer cells by recognizing novel tumor antigens and stimulating adaptive and innate immune effector responses intended to eliminate cancer cells before they can cause disease. Cancer essentially arises as a consequence of abnormal and invasive cell proliferation and cell survival (i.e., tumor growth). The process by which normal cells are transformed into cancer cells is called **carcinogenesis**. A normal cell becoming a disease-causing cancer cell involves a multistage process that entails the accumulation of numerous independent mutations, which individually have escaped the cell's intrinsic safety mechanisms for repairing mutated DNA and/or causing abnormally behaving cells to die by apoptosis (aka, programmed cell death or cell suicide). Characteristics of the transformation process include alterations in cellular morphology, growth characteristics and biochemical properties, including changes in protein expression in ways that make the cancer cell appear foreign to the immune system (i.e., by expressing tumor antigens). In order to understand carcinogenesis (i.e., how a normal cell becomes a disease-causing cancer), one must understand **immunosurveillance**, the ability of the immune system to recognize and destroy cancer cells, and **immunoediting**, the process by which successful tumors evade immunosurveillance.

### **6.4.1 Immunosurveillance**

The ability of the immune system to recognize and destroy cancer cells is known as **immunosurveillance** or cancer immunosurveillance (Finn, 2018). Through the mechanisms of immunosurveillance, most potentially cancerous cells are identified and eliminated before they can cause harm—only a small minority of such cells are able to proliferate, survive, and give rise to clinical disease. Those that do develop into clinical cancer do so by avoiding destruction by the immune system.

For example, CTLs (CD8+ cytotoxic T lymphocytes) can recognize cancer cells and infiltrate the tumor microenvironment thereby recognizing and killing cancer cells expressing tumor antigens on their cell surfaces. In many cancers, including bladder cancer, infiltration into the tumor microenvironment of CD4+ helper T cells producing Th1-like cytokines (e.g., IL-2, TNF- $\alpha$  and IFN- $\gamma$ ) as well as activated CD8+ CTLs and NK cells producing soluble cytotoxins (e.g., granzymes, perforin) associates with a favorable prognosis (Joseph & Enting, 2019; Clemente et al., 1996; Oldford et al., 2006; Dieu-Nosjean et al., 2008; Kusuda et al., 2005; Tosolini et al. 2011; Vesalainen et al., 1994; Ubukata et al., 2010; Fridman et al., 2012; Kitamura et al.; 2015); and (Kondo et al., 2006).

Some mutated cells are able to avoid destruction by the immune system. Indeed, the avoidance of immune detection and elimination is a hallmark of cancer progression. Answering the question of how cancer cells avoid destruction by the immune system requires understanding the complexity of how cancer cells and the immune system both evolve within the changing tumor microenvironment. Paradoxically, through pro-inflammatory processes, the immune response can both destroy cancer cells (i.e., good inflammation) and, conversely, promote tumor progression by shaping tumor immunogenicity and suppressing anti-tumor immunity. (i.e., bad inflammation).

### ***6.4.2 Inflammation***

Normal physiologic inflammation is a tightly regulated process involving, among other things, the recruitment of phagocytic cells and the production of soluble inflammatory mediators (e.g., cytokines) that facilitate the destruction and removal of harmful agents from the body. Characteristics of inflammation include redness (caused by increased blood flow to the affected area), swelling (caused by accumulation of fluid in the affected area), pain (caused by release of inflammatory mediators that activate pain receptors), and heat (caused by increased blood flow to and metabolic activity in the affected area). A benefit of discomforts characteristic of inflammation is that they enable the cells and soluble mediators of the immune system to be brought rapidly and in large numbers to the infected or affected tissue. Inflammation is a normal protective process that, when controlled properly, resolves once the potential for harm has been eliminated.

Unresolved inflammation (also called dysregulated inflammation or chronic inflammation) is a characteristic linked to the development or progression of numerous chronic disorders and diseases—including cancer. In essence, “good” inflammation (i.e., acute inflammation) occurs when it acts as part of a defense mechanism to heal injuries or fight infections by causing the physiological changes (e.g., redness, swelling, heat, pain, etc.) that facilitate recruitment of phagocytes and other white blood cells to the affected area. “Bad” inflammation (chronic inflammation) may occur when it persists even after the initial threat has been resolved, when the response is not proportional to the magnitude of the

threat, or when inflammation occurs in the absence of a clear trigger (Oronsky et al. 2022).

Phagocytosis is the process by which certain white blood cells (i.e., phagocytes) surround, engulf, and destroy foreign substances, such as bacteria, dead cells, and other particles, thereby protecting the body against foreign invaders. The destruction of the foreign substance by the phagocyte involves a transient increase in oxygen consumption known as the 'respiratory burst,' which involves the production of various toxic reactive oxygen species (ROS). This respiratory burst is an example of normal ROS formation playing a beneficial and protective role within the body. However, when the ROS products from the respiratory burst leak out of the phagocytes or become imbalanced by overcoming normal antioxidant measures, this can cause damage, mediated by oxidative stress and pro-inflammatory processes, to the surrounding tissues.

#### **6.4.3 Oxidative Stress**

Oxidative stress occurs when there is an imbalance of free radicals (i.e., unstable molecules) and antioxidants in the body that can cause damage to cells). When there is an over production of ROS, an organism is thought to be in oxidative stress, resulting in damage to cellular macromolecules including nucleic acids (e.g., DNA), proteins and lipids (Reddy, 2023; Ghezzi et al., 2017).

One theory of disease posits that free radical reactive molecules build up in the body over time and lead to cellular damage, which plays a key role in the development and progression of various diseases including cancers. Many studies in cell systems have found antioxidants to be effective at preventing damage. Early work in this area led to the belief that antioxidants prevent disease and promote human health resulting in increased consumption of antioxidant supplements. However, early *in vivo* findings in animals have called this into question. For example, in laboratory experiments performed using a nematode *C. elegans* genetically engineered to overproduce free radicals, lifespans did not differ from controls (Doonan et al., 2008). Additionally, mice engineered to overproduce antioxidants didn't live any longer than their control counterparts (Perez et al, 2009). In humans, one study found antioxidant supplements counteracted the health-promoting effects of exercise (Ristow et al., 2009), and evaluation of 56 randomized clinical trials with a low risk of bias found that antioxidant supplements were actually associated with higher mortality (Bjelakovic et al., 2013a; 2013b). The point here is that the *sin qua non* viewpoint that all chemical exposures increase oxidative stress, thereby being a plausible mechanism of disease is unfounded.

#### **6.4.4 Immunoediting**

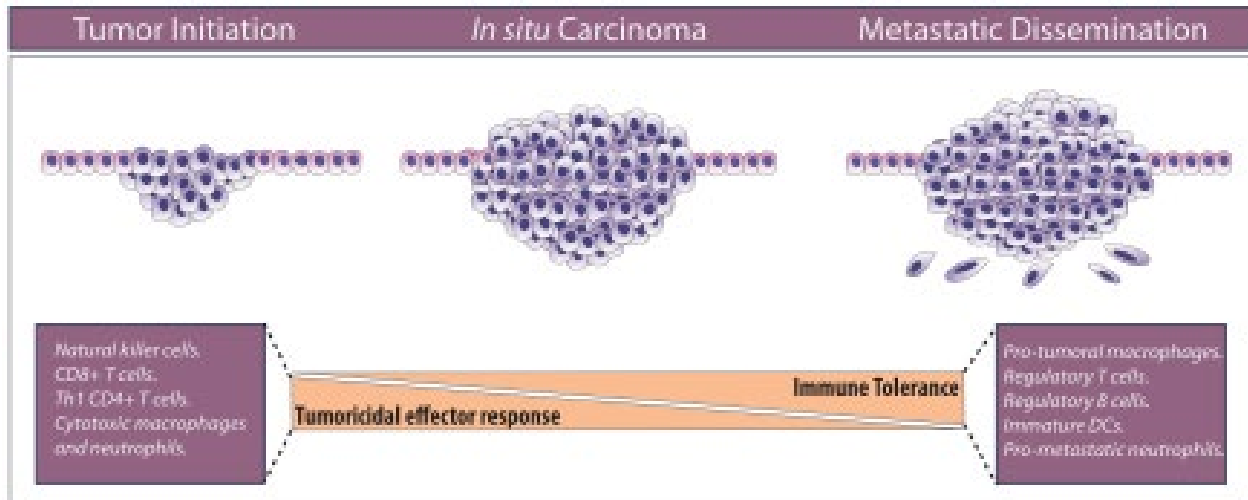
The duality of the immune system in combating and promoting tumor growth is called cancer **immunoediting**. Cancer immunoediting consists of three phases, known as the

"three E's," which are i) **elimination**, ii) **equilibrium**, and iii) **escape** (Teng et al., 2015; Fridman et al., 2011; 2012; 2013).

In the first **elimination** phase, innate and adaptive immunity work in concert to recognize and destroy developing tumors before they become clinically apparent. During the second **equilibrium** phase the outgrowth of rare tumor cell variants that survived elimination is held in check by the immune system, thereby establishing a balance between immune system and tumor cells. In the third and final phase, **escape**, the abnormal growth of tumor cells eventually escapes control of the immune system, thereby leading to malignancy. The mechanisms by which tumor cells escape control by the immune system include 1) downregulation of tumor antigens or loss of mechanisms that facilitate antigen presentation to T cells (i.e., loss of immune recognition); 2) upregulation of resistance mechanisms against the cytotoxic effectors of immunity (i.e., loss of immune system functions that destroy pathogens and remove them from the body) or upregulation of pro-survival or growth factor genes (i.e., outrunning the immune system's ability to destroy and eliminate pathogens), and 3) establishment of an immunosuppressive tumor microenvironment (i.e., chronic inflammation) through increased or changed production of inhibitory cytokines and growth factors (e.g., VEGF, TGF- $\beta$ ), induction or recruitment of functional immunosuppressive cells (e.g., Tregs, MDSCs, M2 macrophages), or induction of adaptive immune resistance by stimulating inhibitory receptors (i.e., immune checkpoints) on immune effector cells.

The following figure depicts that tumor progression is accompanied by changes in the tumor microenvironment whereby over time immune effector functions change from being tumoricidal to being tolerogenic.

**Figure 6. Roles Of The Immune System In Cancer: From Tumor Initiation To Metastatic Progression (Gonzalez et al., 2018).**



Immunoediting demonstrates that the immune system has both pro-tumorigenic and anti-tumor effects, the balance between the two influencing the progression of an individual tumor. This balance is illustrated in Figure 6, which shows that potential upregulation vs. downregulation of various immune effector functions can have a negative effect, a positive effect, or no effect depending on when during the carcinogenic progression they act.

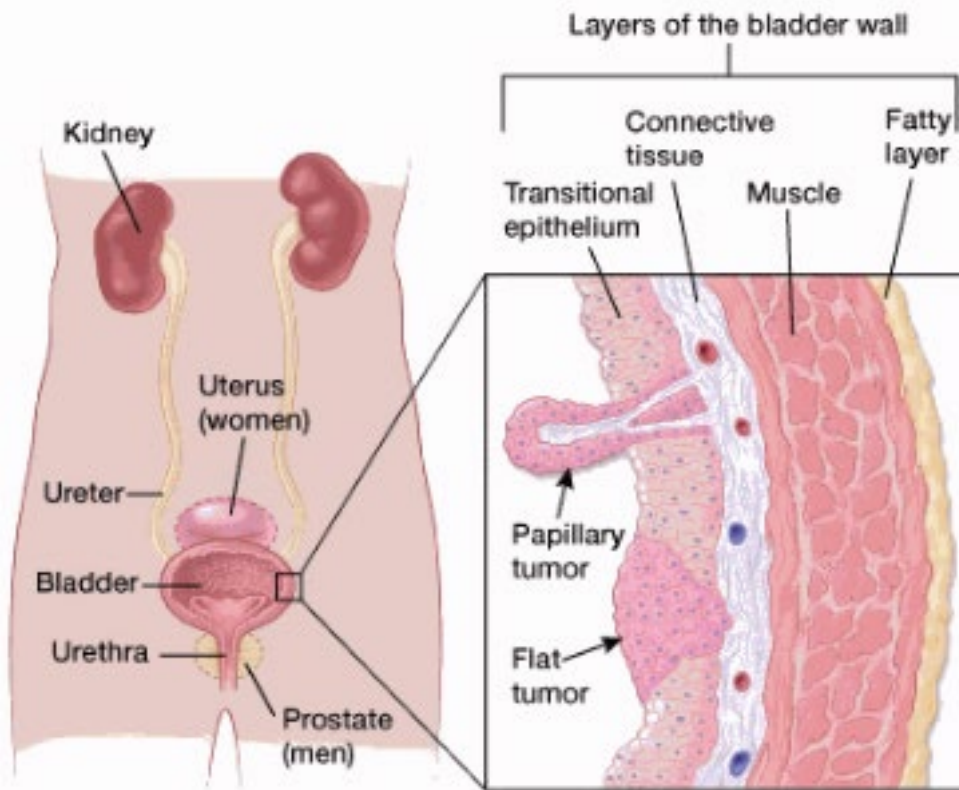
## 6.5 The Role of the Immune System in Bladder Cancer

Bladder cancer is also known as urothelial carcinoma or transitional cell carcinoma (TCC). Urothelial carcinoma is a cancer that begins in the urothelial cells—the epithelial tissue that lines the urinary tract, which consists of the urethra, bladder, ureters and renal pelvis. The walls of the urinary tract consist of this epithelial cell layer (i.e., urothelium), which lines the lumen of the bladder, followed by a layer of fibroconnective tissue and blood vessels (i.e., lamina propria), a thick layer of muscular bundles (i.e., muscularis propria), and a perivesical fat layer (Fig. 7).<sup>26</sup>

**Figure 7. The Layers of the Bladder Wall**

<sup>26</sup> <https://www.cancer.org/cancer/types/bladder-cancer/about/what-is-bladder-cancer.html>





Cancer in the transitional epithelial layer (i.e., urothelial cancer) is the most common form of bladder cancer affecting ~95% of patients (Lenis et al., 2020; Lokeshwar et al., 2022; Jubber et al., 2023; Dyrskjot et al., 2023; Yang et al., 2024). At diagnosis, urothelial cancer is characterized as either non-muscle-invasive bladder cancer (NMIBC; stages Tis, Ta and T1) or muscle-invasive bladder cancer (MIBC; stages T2-T4). As the name implies, NMIBC has not grown into the muscle layer of the urinary tract, whereas MIBC has grown into the muscle layer. MIBC can spread more easily and tends to be more difficult to treat.

Bladder cancer is the fourth most common cancer in males, and much more uncommon in females.<sup>27</sup> It makes up about 4% of cancer diagnoses in the United States with estimates of more than 82,000 new cases of bladder cancer and nearly 17,000 deaths from the disease reported in 2024. Thus, there is a clear gender difference both in incidence and prognosis for bladder cancer. Advanced age is the greatest risk factor for bladder cancer, with an average age of diagnosis between 70 and 84 years—90% of people with bladder cancer are older than age 50. There appears to be a positive familial predisposition to

<sup>27</sup> <https://www.cancer.org/cancer/types/bladder-cancer/about/key-statistics.html>

bladder cancer as evidenced by the report of an association between bladder cancer risk for study participants who had a first-degree relative with bladder cancer (OR=1.8, 95% CI:1.2,2.9) or a sibling with bladder cancer (OR=2.6, 95% CI:1.3,5.3) (Koutros et al., 2021). Thus, intrinsic factors (e.g., genetics, age, gender) appear to be prominent as risk factors associated with bladder cancer causation.<sup>28</sup> The association between advanced age and bladder cancer incidence likely is attributable to age-related reduction in DNA repair mechanisms (Shariat et al., 2009).

Bladder cancer also has been associated with a variety of external risk factors (Jubber et al., 2023), the most prominent of which is the use of tobacco products (i.e., smoking cigarettes, cigars or pipes).<sup>29</sup> The mode of action underlying smoking risk in bladder cancer appears to be the accumulation of harmful chemicals and metabolites in the urine, which may damage the lining of the bladder resulting in carcinogenic initiating events. There is sufficient evidence that certain occupational chemical exposures—particularly for workers in the dye and rubber manufacturing industries—have increased bladder cancer risk.<sup>30</sup>

The immunobiology of the bladder both in health and disease is complex (Joseph & Enting, 2019). A variety of immune cell populations, both innate and adaptive, play a role in the immune response to bladder cancer. The interactions between these different immune cells, as well as interactions between them and the tumor cells and stromal elements, evolve in intricate ways that shape the tumor microenvironment over time resulting either in tumor regression or progression. An example of the complex interactions that take place is seen with BCG treatment (Fig. 8).

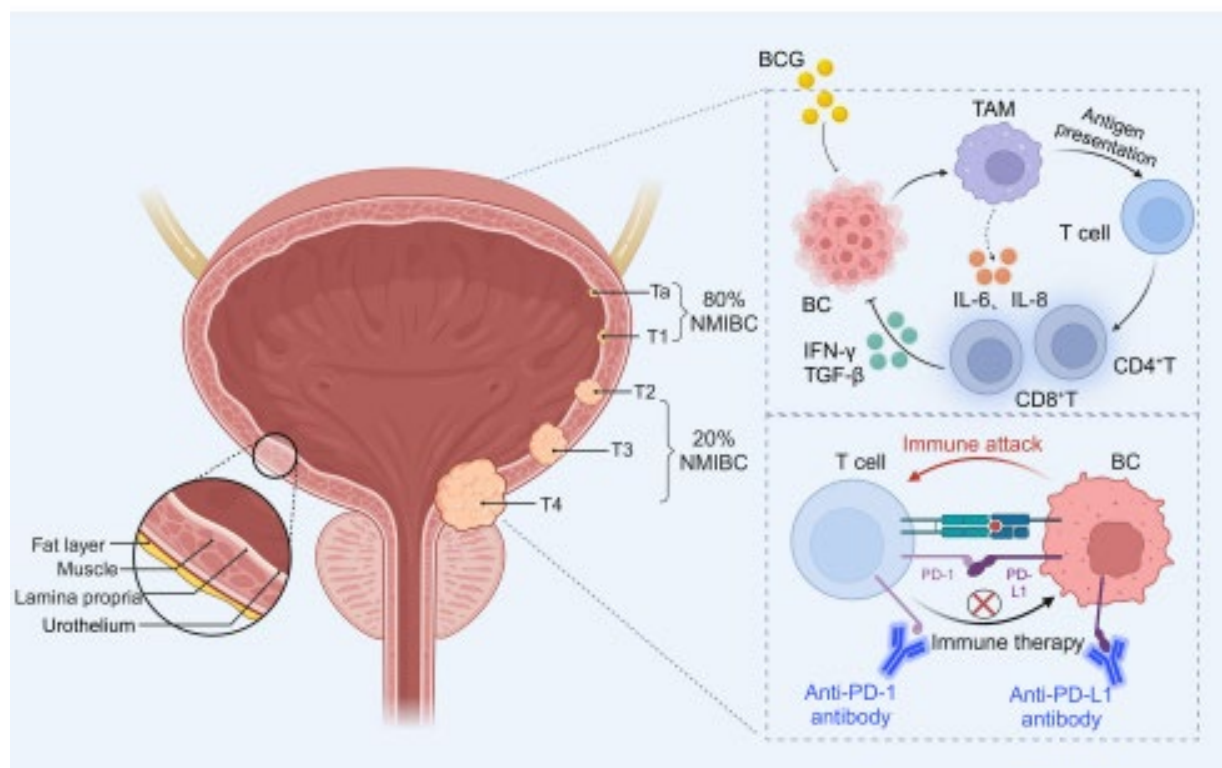
---

<sup>28</sup> Dr. Gilbert misinterpreted or overstated the findings of Koutros et al., 2021 by claiming that it evidenced that “... *bladder cancer relies more on environmental than genetic contributions.*” Gilbert Bladder Cancer Report, p. 10. Koutros (2021) focused on familial association and did not compare the relative contributions of environmental and genetic factors to bladder cancer risk.

<sup>29</sup> <https://www.mayoclinic.org/diseases-conditions/bladder-cancer/symptoms-causes/syc-20356104>

<sup>30</sup> Dr. Gilbert cited Jubber et al., 2023 claiming it to be a source supporting that exposure to environmental and workplace related chemicals are one of the most important extrinsic risk factors for bladder cancer. Gilbert Bladder Cancer Report, p. 10. Notably, Jubber (2023) indicates that there is limited evidence of an association between tetrachloroethylene (PCE) exposure and bladder cancer risk.

**Figure 8. Left, Grading of bladder cancer based on extent of invasiveness (Ta - T4). Right top, BCG stimulation of the immune response; Right bottom, Immune checkpoint therapeutic targets (Yang et al., 2024).**

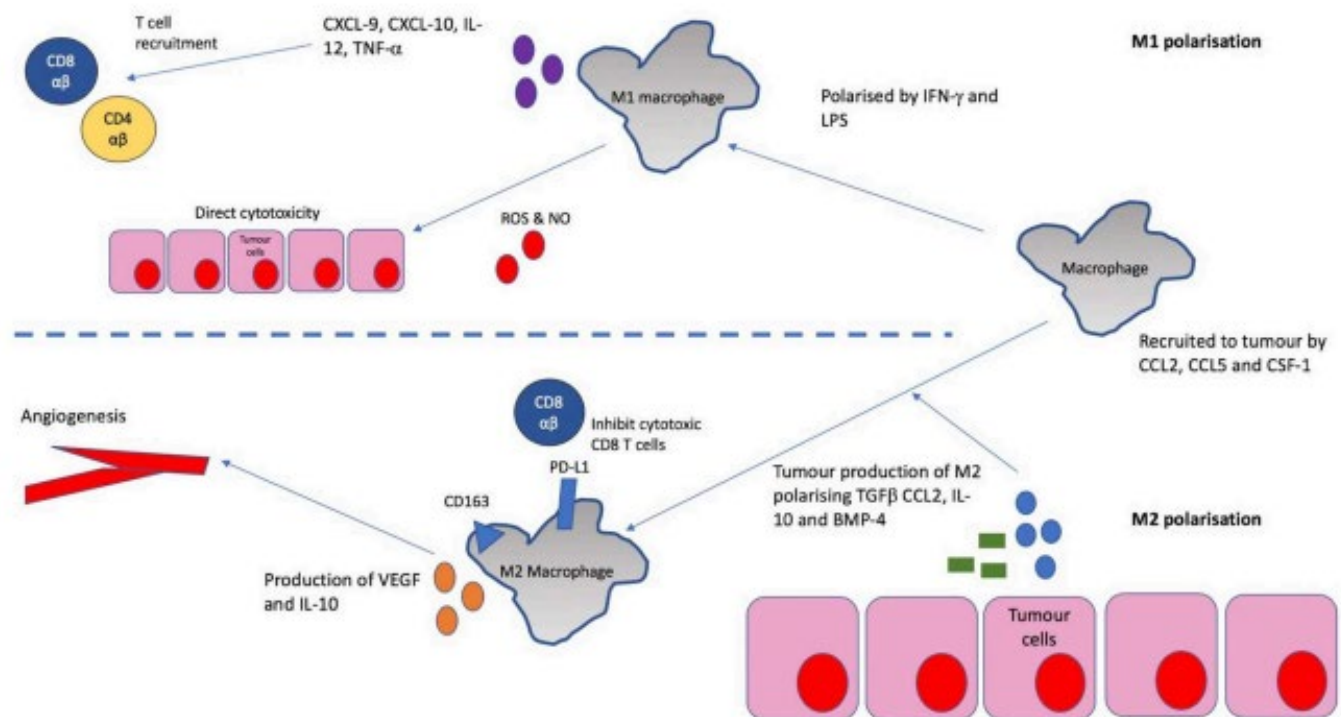


BCG acts to destroy tumor cells through processes that include apoptosis, necrosis, inflammation, and oxidative stress. These activities stimulate tumor-associated macrophages (TAMs) to produce pro-inflammatory cytokines and chemokines such as IL-6 and IL-8, which, together with antigen presentation to CD4<sup>+</sup> T cells, upregulates the tumoricidal activities of CD8<sup>+</sup> cytotoxic T cells through mechanisms that include release of the cytokines IFN- $\gamma$  and TGF- $\beta$ . As will be discussed in a later Section (6.6.1.3), some studies—particularly with autoimmune prone mice—suggest that TCE immunotoxicity involves effects on some of these same cell subsets (e.g., CD4<sup>+</sup> T cells) and mediators (e.g., IL-6, IFN- $\gamma$  and TGF- $\beta$ ). As will be developed more in detail later in this report, it is my opinion that the immunotoxic effects of TCE observed with autoimmune prone mice are not generalizable to the etiology of bladder cancer. Rather than supporting that these effects of TCE would cause bladder cancer, they suggest, to the contrary, that TCE immunomodulation could be protective at the early stages of bladder cancer tumorigenesis.

As discussed above in Section 6.4.4, a characteristic hallmark of tumor progression is the ability of cancerous cells to evade destruction by the immune system. In large measure, evasion of the immune system by cancer cells occurs because the activities of CD4<sup>+</sup> T helper

cell subtypes change from those that are anti-tumor to those that are pro-tumor within the tumor microenvironment. In many cancers, including bladder cancer, these changes in the activities of different T cell subpopulations are accompanied by changes in the innate immune system—namely, with subtypes of macrophages called M1-macrophages and M2-macrophages (Fig. 9).<sup>31</sup>

**Figure 9. Polarization of Macrophage Sub-populations in Bladder Cancer (Joseph & Enting, 2019).**



M1-macrophages are mainly anti-tumor either through direct tumor cell cytotoxicity via the formation of reactive oxygen species, or indirectly through the production of chemokines and cytokines (e.g., IL-12, TNF-α) that promote the activities of CD4<sup>+</sup> Th1 cells and CD8<sup>+</sup> cytotoxic T cells. M2-macrophages are mainly pro-tumor due to their production of cytokines (e.g., IL-10, TGF-β, etc.), angiogenic factors (e.g., VEGF) and expression of immune checkpoint proteins (e.g., PD-L1), which together with the recruitment of immunosuppressive T-Reg cells into the tumor microenvironment, facilitate tumor

<sup>31</sup> M1 and M2 macrophage subpopulations were named to mirror the Th1-Th2 dichotomy described for CD4<sup>+</sup> T cells).

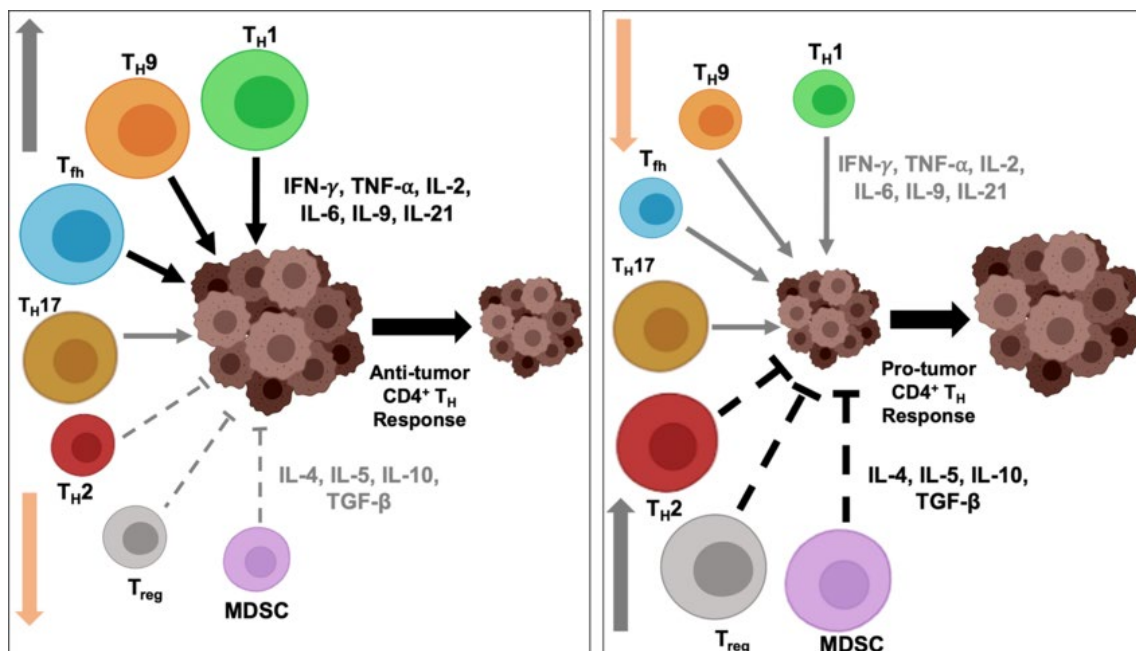
progression. Of note, in a murine model of TCE-induced liver injury, dermal exposure to TCE induced resident macrophages in the liver (i.e., Kupffer cells) toward the M1 phenotype in a TNF- $\alpha$  dependent manner (Zhang et al., 2022).

### ***6.5.1 Plaintiffs' Experts' Proposed Mechanistic Interconnections between TCE or Other VOCs and Bladder Cancer***

The vast majority of patients with bladder cancer are not known to have experienced appreciable exposure to TCE, PCE, benzene, or vinyl chloride alone, or in combination with one another. The vast majority of people who have been exposed to TCE, even at high levels, are not known to have developed bladder cancer. Moreover, the vast majority of people who have been exposed to TCE, even at high levels that may occur in occupational settings, have not been shown to display clinically apparent immune dysfunction. Hence, the characteristic polarization of the immune response that is characteristic of bladder cancer progression occurs independent of TCE exposure or exposure to other VOCs found at Camp Lejeune.

In addition, anti- versus pro-tumorigenic CD4<sup>+</sup> helper T cell activities determine bladder cancer progression versus regression (Fig. 10).

**Figure 10. CD4<sup>+</sup> T cell Subtypes and Tumor Regression/Progression (Basu et al., 2021).**



In the Section that follows, which details what is known about TCE immunotoxicity from human and animal studies the collective data shows that, contrary to plaintiff's experts'



opinions, TCE perturbation of various immune system components align more with anti-tumor effects than with pro-tumor effects.

## **6.6 Immunotoxicity**

Immunotoxicology is broadly defined as the study of the adverse effects of exposures to environmental, occupational, or therapeutic agents on the immune system. Conceptually, these adverse effects could either be due to immunosuppression or immune stimulation.

### ***6.6.1 TCE Immunotoxicity***

There is an extensive scientific literature concerning TCE and its posited effects on the immune system (Ordaz et al., 2017), but much of the literature concerning the immunotoxicity of TCE comes from observations made with human subjects who were exposed to TCE in the workplace, usually at high levels, or from experimental studies with animals, usually mice, oftentimes dosed with high levels of TCE following which various immune endpoints have been measured.

In recent years, the immunostimulatory effects of TCE exacerbating systemic autoimmunity, particularly in murine models, has garnered much attention. The mechanisms whereby TCE may contribute to the pathogenesis of autoimmune disease in genetically prone strains of mice include epigenetic modifications, systemic inflammation, pro-inflammatory cytokines, and increased oxidative stress. The value of studying TCE in autoimmune prone mice lies less with environmental relevance and risk assessment, but more with having an inducible animal model of systemic autoimmunity, where these mechanistic features attributable to autoimmune disease etiology, in general, can be studied. Owing to the inherent intricacies of the immune system with its various checks and balances (i.e., immunoregulatory mechanisms), the etiology and pathogenesis of autoimmune diseases involve highly complex processes. Both genetic (i.e., intrinsic) and environmental (i.e., extrinsic) factors have been implicated as risk factors in autoimmune diseases—like most chronic diseases the etiology of autoimmune diseases is complex and multifactorial. Cancers, including bladder cancer, also are complex multifactorial chronic diseases. Although there may be some overlap between the intrinsic and extrinsic factors etiologically involved in autoimmune diseases and cancers, there are as many differences—likely more—as there are similarities. There are hundreds of different autoimmune diseases, which are similar enough that they can be classified as such, but they have distinct pathologies and different intrinsic and extrinsic factors involved in their etiologies. The immunotoxicology literature does not implicate TCE causatively in all autoimmune diseases—interpreting it as being so would require a leap in logic that ignores the complexity and multifactorial basis of each disease and their differences. It follows, then, based on the existing knowledge base and gaps in same, that a similar leap in logic would be required to implicate TCE immunomodulation as a

mechanistic basis of any of the hundreds of different cancers—including bladder cancer.

#### **6.6.1.1 Human Studies**

Federal and international agencies have concluded that the immune system is a *potential* target of TCE toxicity, but there is no evidence for a mode of action, immune or otherwise, by which TCE causes bladder cancer. The following sections provide a comprehensive discussion of studies that have explored the effects of TCE on the immune systems of humans and animals (mostly rodents). The findings from these studies are not generalizable, as plaintiffs' experts opine, to informing that TCE causes bladder cancer by affecting the immune system. The scientific literature does not support that TCE immunotoxicity has been linked to bladder cancer, and that claim has not been made in any peer-reviewed scientific studies.

The amassed scientific literature concerning TCE and the human immune system, including the studies listed by Dr. Gilbert in Table II of her report (all of which, and more, are addressed below), does not support the hypothesis that TCE causes bladder cancer through immune/inflammatory mechanisms. Dr. Gilbert simply listed eight studies concerning effects of TCE exposure on immune parameters in human subjects (Gilbert Bladder Cancer Report, p. 21). She provided no analysis, discussion or critique of the individual papers or collective literature. Summarized in Table 1 below are my conclusions as to these human studies, which is followed by a more in-depth discussion of each study.

**Table 1. Human Studies Concerning TCE Immunotoxicity**

<i>Study</i>	<i>My Conclusions</i>
<b>1) Iavicoli et al., 2005</b>	Given the observation that Th1 cytokines were increased in the TCE-exposed workers, these findings do not align with the premise that TCE causes bladder cancer through perturbations of the immune system. To the contrary, these results suggest that, rather than promoting tumor progression, exposure to TCE could foster a protective immune response by promoting the early infiltration into the tumor microenvironment of CD4+ helper T cells producing Th1-like cytokines.
<b>2) Zhang et al., 2013</b>	Based solely on their levels of serum immunoglobulins, which were the only immune data measured, the vast majority of the subjects in this study, irrespective of their TCE exposure, were immunocompetent—not immunodeficient or immunosuppressed. This study falls far short of supporting the conclusion that TCE causes human bladder cancer by affecting immunological mechanisms.
<b>3) Lee et al., 2019</b>	The findings of this study concerning the modest decrease in the CD4+ effector memory cell compartment in TCE-exposed subjects compared to controls, which also was not found to be dose-dependent, is not generalizable to immune control of bladder cancer, and does not stand as evidence supporting that posited, but unverified, effects of TCE on TEM cells are mechanistically tied to bladder cancer causation. More pointedly, there were no known reports of bladder cancer arising in

	any of the low TCE-exposed subjects in this study.
<b>4) Lan et al., 2010</b>	These findings do not support a conceptual framework that alterations of the immune system due to TCE exposure cause bladder cancer by affecting immunological mechanisms.
<b>5) Hosgood et al., 2012</b>	No comments were made by the authors that the findings support an association between TCE and bladder cancer. The authors stated that caution should be used when interpreting the study findings until confirmed in additional studies given the small sample size and the potential confounding from additional factors that could influence lymphocyte cell counts.
<b>6) Bassig et al., 2016</b>	The data in this study show that the vast majority of the subjects in this study across the exposure groups, ranging from control to low-TCE to high-TCE, fall within <i>normal</i> counts for circulating B cells as well as other lymphocyte subpopulations that were assessed. Thus, this study does not provide evidence that TCE is mechanistically tied to bladder cancer through immunosuppression.
<b>7) Bassig et al., 2013</b>	The finding that TCE-exposed workers have reduced IL-10 runs <i>counter</i> to the proposition that TCE causes bladder cancer through perturbation of the immune response.
<b>8-10) Zhang et al., 2017; Jia et al., 2012; Xuequin et al., 2018</b>	These three OMDLT studies show differing and, in the case of the Jia and Xuequin studies, opposite results. Therefore, they are not generalizable to support the leap in logic that inflammation in other contexts—such as bladder cancer—is caused by TCE exposure.
<b>11) Kamijima et al., 2013</b>	These findings detail how the immune system reacts specifically to latent herpes virus reactivation, which is not relevant to the immunobiology of bladder cancer.
<b>12) Li et al., 2019</b>	The findings from this study are not generalizable to the immunobiology of bladder cancer, and if they were to be taken so, they more aptly support the hypothesis that TCE exposure promotes bladder cancer regression through activation of Th1-mediated immunity.

1) Iavicoli et al., 2005.<sup>32</sup>

In this study of Guangdong, China factory workers, Iavicoli reported statistically significant differences in serum levels of certain cytokines between TCE-exposed factory workers and controls. The TCE-exposed subjects worked in the printing sector and had been exposed to TCE from degreasing processes at a mean workplace air concentration of  $35 \pm 14$  mg/m<sup>3</sup> (6.3 ppm) for at least 3 years. Thus, inhalation of TCE (i.e., presence of TCE in the breathing zone) was the primary route of exposure to TCE for these subjects, although other routes (e.g., dermal) also could have occurred. The workers' exposures to TCE were confirmed by monitoring their urinary levels of trichloroacetic acid (TCA)—a metabolite of TCE.

---

<sup>32</sup> Dr. Gilbert did not include Iavicoli et al., 2005 in her list of epidemiological studies of TCE and immunotoxicity.



Comparisons were made between the serum levels of cytokines for the TCE-exposed workers and an “internal control group” (i.e., workers from the same factory who performed the same job functions but did not engage in degreasing processes and were not near sources of TCE within the factory) as well as an “external control group” (i.e., office workers from the same factory who were not exposed to any known occupational sources of TCE). Although immune function was not assessed in this study, the results showed that the levels of interleukin-2 (IL-2) and interferon- $\gamma$  (IFN- $\gamma$ ), which are Th1-like cytokines, were significantly increased in the TCE-exposed workers compared to controls, while the levels of interleukin-4 (IL-4), which is a Th2-like cytokine, were significantly decreased in the TCE-exposed workers compared to controls. **Thus, given the observation that Th1 cytokines were increased in the TCE-exposed workers, these findings do not align with the premise that TCE causes bladder cancer through perturbations of the immune system. To the contrary, these results suggest that, rather than promoting tumor progression, exposure to TCE could foster a protective immune response by promoting the early infiltration into the tumor microenvironment of CD4+ helper T cells producing Th1-like cytokines.**

2) Zhang et al., 2013.

In another study of Guangdong, China factory workers exposed to TCE, Zhang (2013) observed statistically significant decreased levels of serum immunoglobulins (IgM and IgG, but not IgE) for TCE-exposed subjects relative to controls, who had not been exposed to any known source(s) of TCE. The study design consisted of high and low TCE exposure groups based on air monitoring results during the month prior to serum immunoglobulin assessment. The high exposure group was characterized as having TCE exposure exceeding 12 ppm (mean TCE  $38.4 \pm 44.6$  ppm) in air, and the low exposure group was characterized as having TCE exposure below 12 ppm (mean TCE  $5.2 \pm 3.2$  ppm) in air. A control population (i.e., “TCE-unexposed”) comprised of subjects who did not have any known TCE exposure history was included in the study design. Workers exposed to TCE had a 17.5% decrease and a 38% decrease in the reported levels of IgG and IgM, respectively, relative to the levels measured in control, TCE-unexposed subjects. The magnitudes of the decreased values were similar in workers exposed to low and high levels of TCE, and the reduced levels of serum immunoglobulins did not correlate with decreased B cell counts that the study authors had previously reported for the same TCE-exposed workers (Lan et al., 2010). Like most of the descriptive cross-sectional studies that have compared immune endpoints between TCE-exposed and control subjects, this study lacked any functional assessment of immunocompetence. The study authors speculated that the lower levels of serum immunoglobulins found in the TCE-exposed subjects may be indicative of reduced immune capacity or greater susceptibility to infection, but they had no data to support this premise.

Susceptibility to cancer was not mentioned, which, perhaps, is notable in view of the fact that the study was published in the journal *Carcinogenesis*.

In short, although this study appears to show statistically significant reduced levels of serum immunoglobulins in TCE-exposed subjects relative to controls, the demonstrable biological relevance of the finding is difficult to grasp. The normal levels of serum immunoglobulins in humans are quite variable with IgG ranging between 700 to 1600 mg/dL and IgM ranging between 40 to 230 mg/dL (Dati et al., 1996). Although the data in the Zhang study are presented as box and whisker plots and in different units (i.e.,  $\mu\text{g/mL}$  instead of mg/dL—the norm for clinical lab reporting), the vast majority of the subjects in this study across the exposure groups, ranging from control to low-TCE to high-TCE, fall within normal serum IgG and IgM ranges. **As such, based solely on their levels of serum immunoglobulins, which were the only immune data measured, the vast majority of the subjects in this study, irrespective of their TCE exposure, were immunocompetent—not immunodeficient or immunosuppressed. Thus, the Zhang study falls far short of supporting the conclusion that TCE causes human bladder cancer by affecting immunological mechanisms.**

3) Lee et al., 2019.

The Lee study also reported on effects of occupational TCE exposure on serum immunoglobulin levels based on the same worker populations assessed in Zhang (2013), but the study design changed slightly by defining the low TCE-exposed and high TCE-exposed populations as below 10 ppm and above 10 ppm, respectively, to align with international occupational TCE exposure standards—with 10 ppm purported to be a common regulatory standard. The data showed statistically significant decreased levels of serum IgG and IgM in the TCE-exposed workers relative to controls. For the control group the IgG level was  $1,099 \pm 297$  mg/dL and the IgM level was  $118 \pm 82$  mg/dL. For the low (i.e., < 10 ppm) TCE group the IgG level was  $924 \pm 166$  mg/dL and the IgM level was  $76 \pm 34$  mg/dL. Finally, for the high (i.e., > 10 ppm) TCE group the IgG level was  $894 \pm 215$  mg/dL and the IgM level was  $71 \pm 37$  mg/dL. Again, given accepted reference ranges for serum immunoglobulins (IgG = 700 to 1600 mg/dL, and IgM = 40 to 230 mg/dL), based on their reported serum IgG and IgM levels, irrespective of TCE exposure, the subjects in this study were immunocompetent (i.e., they had normally functioning immune systems)—not immunodeficient or immunosuppressed. There is no evidence that the TCE exposed subjects in this worker population demonstrated any indications of immune dysfunction ranging between functional immunosuppression (i.e., hypo-immunity) and chronic inflammation (i.e., hyper-immunity).

This study also showed a modest, but statistically significant, decreased number of what are known as CD4+ effector memory T cells (i.e.,  $T_{EM}$  cells) between controls and

subjects in the low TCE exposure group. The effect was not dose dependent, in that, significantly lower  $T_{EM}$  cells were found only in the low TCE exposure group and not the high TCE exposure group. For the control group, the  $CD4+ T_{EM}$  count was  $224.9 \pm 92.9$ . For the low (i.e.,  $< 10$  ppm) TCE group the  $CD4+ T_{EM}$  count was  $181.8 \pm 56.7$ . Finally, for the high (i.e.,  $> 10$  ppm) TCE group the  $CD4+ T_{EM}$  count was  $184 \pm 86.1$ . The study authors speculated that a decrease in the number of  $CD4+$  effector memory cells could lead to a decreased capacity of the body to respond to antigenic-related inflammation, but they had no data to support their premise. For example, TCE-exposed subjects were not demonstrated to have any immune-mediated disorders that tie to insufficient immune memory.<sup>33</sup>

It is improbable that the workers, both TCE-exposed and unexposed, in the Lee study had  $T_{EM}$  cells specific to bladder tumor antigens circulating in their blood. The collection of effector memory T cells that were quantified in each of these subjects represented various unknown antigenic specificities in various unknown states of clonal expansion. **Given these complexities, the findings of the Lee study concerning the modest decrease in the  $CD4+$  effector memory cell compartment in TCE-exposed subjects compared to controls, which also was not found to be dose-dependent, is not generalizable to immune control of bladder cancer, and does not stand as evidence supporting that posited, but unverified, effects of TCE on  $T_{EM}$  cells are mechanistically tied to bladder cancer causation. More pointedly, there were no known reports of bladder cancer arising in any of the low TCE-exposed subjects in this study.**

4) Lan et al., 2010.

Using the same cross-sectional study design as described in the preceding papers, Lan conducted a study with the Guangdong, China factory workers aimed at assessing the effects of TCE exposure on peripheral blood cells including total T cells,  $CD4+$  cells,  $CD8+$  cells and NK cells. Modest, but statistically significant, decreases in the numbers of these cell populations were found in the high TCE-exposed (i.e.,  $> 12$  ppm) group relative to controls but not the low TCE-exposed (i.e.,  $< 12$  ppm) group. Although the data appear to show statistically significant lower cell counts for all lymphocyte subsets in the high TCE-exposed group relative to the control unexposed group, there was no functional immunosuppression assessed in this study. Irrespective of the statistical differences, no functional immunosuppression would be expected based on the findings because the data establish

---

<sup>33</sup> Circulating  $CD4+$  effector memory cells are a subset of  $CD4+$  helper T cells that have developed memory characteristics after encountering an antigen. Having developed memory characteristics, they are poised to rapidly respond to future challenges with the same antigen—given that specificity is a characteristic feature of adaptive immunity and immunological memory. Essentially, upon encounter with antigen in the bloodstream, circulating effector memory T cells activate and migrate to where they are needed and quickly take charge of the fight to ward off the specific antigenic threat imposed on the body.

that the vast majority of the subjects in this study across the exposure groups, ranging from control to low-TCE to high-TCE, fall within *normal* counts for each of the lymphocyte subpopulations tabulated.<sup>34</sup> The normal range (i.e., reference values) for total T cells in blood is 700 to 2508 per mm<sup>3</sup> (a mm<sup>3</sup> is a microliter or µl of blood, not a milliliter or ml as indicated by Dr. Gilbert in Table II of her report—the difference is three orders of magnitude or 1000-fold).<sup>35</sup> Thus, the Lan study data showed that the immune systems of TCE-exposed subjects are normal with respect to peripheral blood lymphocyte subset counts. The data support that the vast majority of the subjects in this study, irrespective of their TCE exposure, are immunocompetent (i.e., have lymphocyte subset counts within normal ranges)—not immunodeficient or immunosuppressed. **As such, these findings do not support a conceptual framework that alterations of the immune system due to TCE exposure cause bladder cancer by affecting immunological mechanisms.**

5) Hosgood et al., 2012.an et al., 2010.

In yet another study based on the Guangdong, China factory workers, Hosgood expanded the analysis to include assessment of the effects of TCE exposure on various T cell subsets such as CD4+ naïve and CD4+ memory T cells, CD8+ naïve and memory T cells, and regulatory T cells. Again, statistically significant modest decreases in cell counts for some of the T cell subsets were found for TCE-exposed workers in comparison to control unexposed subjects. However, no functional assessment of immunocompetence were performed to establish that the observed modest decreases in T cell subset numbers, all of which were within normal reference ranges, were immunomodulatory. The authors concluded that the results of this study provide support for the biologic plausibility that TCE is associated with the risk of NHL, which in my opinion is an overstatement. **No comments were made by the authors that the findings support an association between TCE and bladder cancer. Finally, the authors stated that caution should be used when interpreting the study**

---

<sup>34</sup> Various sources provide information concerning reference values for normal lymphocyte counts in blood. The normal range for CD4+ T cells is 464 to 1721 per mm<sup>3</sup> of blood. The normal range for CD8+ T cells is 135 to 852 per mm<sup>3</sup> of blood. The normal range for B cells is 92 to 515 per mm<sup>3</sup> of blood. Finally, the normal range for NK cells is 82 to 594 per mm<sup>3</sup> of blood. (See for example Apoil et al., 2017 and Table 1 of Supplemental data from Lan et al., 2010). As shown, the normal range for cell counts for each subset are quite broad. Thus, the modest, albeit statistically significant, differences in the lymphocyte subset counts between unexposed controls and high TCE-exposed subjects reported in the Lan study are most likely functionally irrelevant and clinically meaningless.

<sup>35</sup> Although this may have been a simple mistake, the error suggests to me that Dr. Gilbert is not aware of normal reference ranges for lymphocyte subpopulations in peripheral blood, and, therefore, did not recognize that the subjects in this study, irrespective of their TCE exposure, had normal lymphocyte subset counts.

**findings until confirmed in additional studies given the small sample size and the potential confounding from additional factors that could influence lymphocyte cell counts.**

6) Bassig et al., 2016.<sup>36</sup>

These investigators expanded the analysis of the Guangdong, China factory workers to include analysis of TCE effects, and other solvents, on the B lymphocyte compartment. The occupational exposure assessments in these workers included TCE as well as benzene and formaldehyde, which was an interesting addition to the study design because the worker cohort appears to be the same as in other studies (i.e., Lan et al., 2010; Hosgood et al., 2012; Lee et al., 2019; Zhang et al., 2013) where only TCE exposure was mentioned. The results showed that workers exposed to TCE and benzene had modest statistically significant decreases in circulating B lymphocytes and decreased B cell activation marker expression; however, the study design did not evaluate if these changes in B cell numbers correlated with any deficits in humoral immune effector functions. **The data in this study show that the vast majority of the subjects in this study across the exposure groups, ranging from control to low-TCE to high-TCE, fall within *normal* counts for circulating B cells as well as other lymphocyte subpopulations that were assessed. Thus, this study does not provide evidence that TCE is mechanistically tied to bladder cancer through immunosuppression.**

7) Bassig et al., 2013.<sup>37</sup>

In another paper based on factory workers who used TCE for metal, optical lens, and circuit board cleaning, Bassig (2013) reported that, compared to unexposed controls, the serum levels of interleukin-10 (IL-10) was decreased by 70% in workers exposed to TCE. No significant differences in levels of IL-6 or TNF- $\alpha$  were observed for TCE-exposed workers compared to unexposed controls. The authors concluded that since IL-10 plays an important role in immunologic processes, particularly in mediating the Th1/Th2 balance (i.e., it counters the activities of pro-inflammatory cytokines), the finding of reduced serum IL-10 in workers exposed to TCE was evidence of its immunotoxicity. Increased production of IL-10 within the tumor microenvironment induces M2 polarization of macrophages—an immunosuppressive macrophage phenotype that also promotes angiogenesis thereby fostering tumor progression (Yang et al., 2024; Joseph & Enting, 2019). **Thus, the finding that TCE-exposed**

---

<sup>36</sup> Dr. Gilbert did not include Bassig et al., 2016 in her list of epidemiological studies of TCE and immunotoxicity. See Gilbert Bladder Cancer Report.

<sup>37</sup> Dr. Gilbert did not include Bassig et al., 2013 in her list of epidemiological studies of TCE and immunotoxicity. See Gilbert Bladder Cancer Report.

**workers have reduced IL-10 runs *counter* to the proposition that TCE causes bladder cancer through perturbation of the immune response.**

8-10) Zhang et al., 2017; Jia et al., 2012; Xuequin et al., 2018.<sup>38</sup>

The Zhang (2017) study involved a subset of workers exposed to TCE who developed a particular hypersensitivity dermatitis syndrome called occupational medicamentosa-like dermatitis (OMLDT). The disorder occurs in a small fraction of workers extensively exposed to TCE, mainly by inhalation, who develop generalized skin lesions (i.e., rashes), fever, hepatitis, leukocytosis and lymphadenopathy. It is a rare syndrome that occurs in subjects exposed occupationally to high levels of TCE by inhalation. Not surprisingly, given the etiological involvement of systemic inflammation, alterations in various pro-inflammatory cytokines have been described in OMLDT subjects. For example, Jia et al. (2012) showed that the systemic levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and TNF- $\alpha$  were significantly elevated in OMLDT subjects in comparison to control subjects who had not been exposed to TCE. But the Jia study also showed that workers who had been exposed to TCE, but did not have OMLDT, did not have elevated levels of pro-inflammatory cytokines. In another study by Xuequin, OMDLT patients were found to have elevated serum levels of IL-10 and increased T-Reg cell type specific transcription factor expression (i.e., *FoxP3*) relative to TCE-exposed workers who were not OMDLT patients or unexposed controls. Relative to unexposed controls, both TCE exposure groups (i.e., OMDLT patients and non-OMDLT subjects) had significantly decreased serum levels of IL-6 and TNF- $\alpha$  the opposite of what was described in Jia. **These three OMDLT studies show differing and, in the case of the Jia and Xuequin studies, opposite results. Therefore, they are not generalizable to support the leap in logic that inflammation in other contexts—such as bladder cancer—is caused by TCE exposure.**

11) Kamijima et al., 2013.

The Kamijima study examined serum cytokine profiles in OMLDT subjects who had been hospitalized for clinical evaluation of exfoliative dermatitis (i.e., skin rash) caused by reactivation of latent herpes virus. The data were presented as frequencies of hospitalized TCE-exposed patients who had serum cytokine levels more than three standard deviations (3 SDs) above the mean values for healthy workers.<sup>39</sup> A major conclusion of this study was that

---

<sup>38</sup> Dr. Gilbert did not include Zhang et al., 2017 or Xuequin et al., 2018 in her list of epidemiological studies of TCE and immunotoxicity.

<sup>39</sup> The frequencies of patients with serum cytokines more than 3 SDs above the mean of healthy workers were reported as follows: 79% (TNF- $\alpha$  and IL-10), 57% (IL-6), 43% (IFN- $\gamma$ ), and 25% (IL-5). The frequencies of healthy workers with serum cytokines more than 3 SDs above the mean were as follows: 0% (IL-5 and IFN- $\gamma$ ), 2% (IL-6 and IL-10), and 4% (TNF- $\alpha$ ).

the elevated levels of IL-10 and TNF- $\alpha$  correlated with higher viral DNA load and higher anti-herpes virus antibody titers, all of which were associated with exfoliative dermatitis type rash.<sup>40</sup> **These findings detail how the immune system reacts specifically to latent herpes virus reactivation, which is not relevant to the immunobiology of bladder cancer.**

12) Li et al., 2019.

In another study that examined immune endpoints in OMDLT patients in comparison to TCE exposure controls and unexposed worker controls, Li et al., 2019 reported increased numbers of activated CD4+ T cells coupled with increased expression of IL-2, IFN- $\gamma$  and TNF- $\alpha$ , and decreased IL-4 expression in the OMDLT patients. **The findings from this study are not generalizable to the immunobiology of bladder cancer, and if they were to be taken so, they more aptly support the hypothesis that TCE exposure promotes bladder cancer regression through activation of Th1-mediated immunity.**

#### ***6.6.1.2 Summary of Human Studies on TCE Immunotoxicity***

As detailed in the preceding Section, many studies involving human subjects have observed statistically significant but modest differences in components of immunity between TCE-exposed and control subjects. In most instances, the experimental designs of these studies were not particularly sophisticated, did not establish that TCE exposure caused functional immunosuppression or frank immunodeficiency, and were conducted with subjects who had experienced high occupational exposures to TCE. Studies that compared serum immunoglobulins (e.g., Zhang et al., 2013; Lee et al., 2019) and lymphocyte subset counts (e.g., Lee et al., 2019; Lan et al., 2010; Hosgood et al., 2012; Bassig et al., 2016) between TCE-exposed and control unexposed subjects showed that the majority of subjects, irrespective of TCE exposure, had *normal* biomarkers of immunity. Studies that explored apparent changes in cytokine expression profiles, while not generalizable to the immunobiology of bladder cancer, show that TCE exposure may be immuno-protective against bladder cancer through the activities of anti-tumor CD4+ T cells. **As such, the amassed scientific literature concerning TCE and the human immune system supports neither the hypothesis nor the conclusion that TCE can cause bladder cancer through perturbations of the immune response or inflammatory processes.**

---

<sup>40</sup> Dr. Gilbert only included the TNF- $\alpha$  data from Kamijima et al., 2013 in Table 2 of her report. Gilbert Bladder Cancer Report, p. 21.



### 6.6.1.3 *Animal Studies*<sup>41</sup>

The utility of animal studies is that they allow for the testing of hypotheses through experiments that are not possible, or ethical, with humans. Oftentimes, there is more control over experimental variables with animal studies. Most importantly, mice can be genetically modified in order to isolate and study the role that individual genes or gene clusters play in regulating the immune response. There are many similarities in the immune system components in mice and humans, although there also are some important differences.

Animal studies support that TCE may cause or exacerbate certain systemic autoimmune diseases (Cooper et al., 2009; Gilbert 2014). Autoimmune diseases are diseases where the immune recognition event is directed toward self-antigens or the immune effector responses involve unregulated and unchecked chronic inflammation (i.e., diseases in which the body's immune system attacks itself). The mice used in these experimental studies had genetic backgrounds that made them autoimmune disease prone and, often were exposed to doses of TCE aimed to provoke alterations of immunity consistent with autoimmune disease pathogenesis. The genetic backgrounds that make these mice autoimmune disease prone are not known to also make them prone to bladder cancer. Therefore, generalizations cannot be made about the effects of TCE on these mice that are relevant to bladder cancer.

Several studies have shown that exposure to TCE in the drinking water of autoimmune disease-prone mice caused the expansion of effector/memory CD4+ T cells with an interferon- $\gamma$  secreting pro-inflammatory Th1-like phenotype coupled with decreased IL-10 secreting T-Reg cells (Choudhury et al., 2024; Banerjee et al., 2020; Griffin et al., 2000; Liu et al., 2022; Li et al., 2018). Applying these findings to the contexture of the immunobiology of bladder cancer, the expectation is that, by virtue of stimulating Th1-mediated immunity at the early stage of carcinogenesis or inhibiting T-Reg activities later during carcinogenesis, TCE could have a *protective effect* rather than an effect that promotes disease progression. The effects of TCE on the Th1/Th2/Th17/T-Reg paradigm align causatively with autoimmune disease more so than they do with cancer. **The results of experiments showing effects of TCE on CD4+ T cell subsets in autoimmune prone mice do not support a conceptual framework that similar effects lead to bladder cancer in humans. No experiments have been done to address the effects of TCE on the myriad CD4+ helper T cell subsets that influence bladder cancer regression versus progression.**

---

<sup>41</sup> Dr. Gilbert acknowledged that the ability of TCE or the other Camp Lejeune VOCs to cause bladder cancer specifically has not been tested in any animal studies. Gilbert Bladder Cancer Report, p. 13.



It has been shown in a particular autoimmune prone strain of mice called MRL +/+, that exposure to TCE via the drinking water alters the production of the cytokine IFN- $\gamma$  through epigenetic mechanisms (Gilbert et al., 2012; 2016a; 2016b). The posited relevance of this TCE effect found in autoimmune prone mice to the contexture of human bladder cancer is questionable, particularly because IFN- $\gamma$  plays a complex role in the tumor microenvironment by having pro- and anti-tumor effects that can influence tumor progression or regression, respectively (Jorgovanovic et al., 2020). Dr. Gilbert acknowledges that IFN- $\gamma$  is pleiotropic (i.e., has multiple and diverse effects),<sup>42</sup> but then seemingly ignores the significance of this by concluding that TCE effects on IFN- $\gamma$  found in autoimmune prone mice are generalizable in informing a mechanism of TCE-induced bladder cancer.<sup>43</sup> **In the absence of direct experimentation showing that TCE modulation of IFN- $\gamma$  is operant mechanistically in bladder tumor progression, this generalization cannot possibly be made given the complex pro- and anti-tumor effects of IFN- $\gamma$ . There are no studies that show that TCE causes epigenetic changes in the contexture of bladder cancer.**

The older animal literature, which entailed classic immunotoxicity testing, showed effects of high dose administration of TCE on various immune endpoints. For example, Wright et al. (1991) examined the effects of intraperitoneal injection of Sprague-Dawley rats and B6C3F1 mice, at 0, 0.05, 0.5, 5.0 and 10.0 mmol/kg per day for 5 days, on splenocyte counts, B cell and T cell mitogenic responses, and hepatic and splenic NK cell activities. The data showed that NK cell cytotoxicity was significantly decreased in rats and mice injected with TCE, and the response was dose dependent. The authors concluded that the data suggested the possibility that the decreased natural (i.e., innate immunity) cytotoxicity response could explain how TCE caused liver tumors in rodents. **These effects of TCE on NK cell activity have not been repeated in humans exposed to environmentally or occupationally relevant concentrations of TCE.**

Two other peer-reviewed studies reported on TCE exposure and NK activity in mice. Peden-Adams et al. (2006) exposed B6C3F1 mice to 0, 1400 or 14000 ppb TCE in drinking water for 3 or 8 weeks from gestation day zero. No effects of TCE on NK activity were observed. Keil et al. (2009) used a similar exposure design (i.e., 0, 1400 or 14000 ppb TCE in drinking water for 27 or 30 weeks), but compared the effects of TCE exposure on immune endpoints between normal (B6C3F1) and autoimmune prone (NZBWF1) mice. No effects of TCE on NK activity were observed in either mouse strain. The strain specificity of TCE on immunity was also reported by Blossom et al. (2006), who showed that the ability of

---

<sup>42</sup> Gilbert Bladder Cancer Report, p. 20.

<sup>43</sup> Gilbert Bladder Cancer Report, p. 20, Figure 1.

trichloroacetaldehyde hydrate (TCAH), a major oxidative metabolite of TCE, to increase the number of IFN $\gamma$ -producing CD4 $^{+}$  lymphocytes required an autoimmune-prone genetic background. **These findings support that particular gene-environment interactions may drive TCE-induced autoimmune disease in mice but are not readily applicable to predicting how TCE might affect the immunobiology of human bladder cancer.**

The immunotoxicity of TCE was further assessed by Boverhof et al. (2013) in Sprague-Dawley rats after inhalation exposure through evaluation of the antibody response to sheep red blood cells, which is a common assay employed in immunotoxicity testing. In this study, rats were exposed to TCE at 0, 100, 300 or 1000 ppm for 6 hours per day for 20 days. The highest dose (i.e., 1000 ppm) was selected to produce moderate liver and kidney toxicity. Relative to unexposed control animals, a significant (i.e., 70%) decrease in the antibody forming cell response was observed only in the high TCE-exposed group. **These results indicate that TCE was immunosuppressive in rats but only at very high levels of exposure.**

Sanders et al., (1982) examined the effects of TCE exposure on immunity in an outbred strain of mice. CD-1 male and female mice were exposed to TCE via the drinking water at 0.1, 1.0, 2.5, and 5 mg/mL for 4 to 6 months.<sup>44</sup> The immune parameters assessed were humoral immunity, cell-mediated immunity, lymphocyte responsiveness, bone marrow function and macrophage function. The results showed that the immune responses of female mice were more affected than the immune responses of males. Cell-mediated immunity and bone marrow stem cell colonization were inhibited at all doses of TCE, whereas, humoral immunity was only suppressed at the highest doses. **Thus, the immune suppression caused by TCE in this study was gender specific in mice and only occurred at high levels of exposure, the relevance of which to human exposures is highly questionable.**

#### **6.6.1.4 Summary of Animal Studies on TCE Immunotoxicity**

Potential effects of TCE, or any of the other Camp Lejeune VOCs, on the progression of bladder cancer via immune or inflammatory mechanisms has not been studied in any animal models of bladder cancer. The immunotoxicity of TCE, has been explored in rodents under experimental paradigms that support TCE exposure producing both immunosuppressive and immunopotentiating (i.e., immune enhancing) effects. Experimental findings concerning TCE effects on certain immune endpoints in autoimmune disease prone mice are not generalizable for informing how TCE may, or may not, affect immune mechanisms within the tumor microenvironment of humans who have bladder cancer.

---

<sup>44</sup> 5 mg/ml = 5 million parts per billion (ppb); 0.1 mg/mL = 100,000 ppb

Autoimmune disease is not bladder cancer. The accompanying genetic predispositions in autoimmune prone mice exacerbated by TCE are not the same, or sufficiently similar, to the genetic factors linked to human bladder cancer. Moreover, much of the literature concerning effects of TCE on immune responses or inflammatory processes were based on high TCE exposures the environmental relevance of which to humans, in general, and human bladder cancer, specifically, is questionable. Several murine models of bladder cancer have been developed to help elucidate the pathogenic mechanisms involved in disease progression as well as to develop new therapeutic agents (John & Said, 2017; Park et al., 2021; Zhang et al., 2015; Fantini et al., 2018; Desponds et al., 2024). No experiments have been performed with any mouse models of bladder cancer to determine the effects of TCE, PCE or benzene exposure, alone, or in combination, on disease progression or regression.<sup>45</sup>

### **6.6.2 PCE Immunotoxicity<sup>46</sup>**

There are very few studies concerning the immunotoxic effects of PCE in humans, and those that have been conducted do not provide a coherent understanding of potential immunotoxic effects of the role, if any, that PCE perturbation of the immune system may play in any human disease—including bladder cancer.

In a study of Egyptian dry-cleaning workers exposed to  $\leq 140$  ppm PCE for 8 hours/day for  $6.45 \pm 3.62$  years, Emara et al. (2010) reported statistically significant increased cell counts for total white blood cell, total lymphocytes, NK cells, CD4+ T cells, and CD8+ T cells in the PCE-exposed workers in comparison to control unexposed workers. There was no reported significant difference between the two groups in cell counts for neutrophils, eosinophils, total T cells, and B cells. Serum levels of IgG, IgM, IgA were unaffected by PCE exposure, but IgE was significantly increased in the PCE-exposed group. The PCE-exposed workers also had modest increased levels of serum and cellular interleukin-4. The authors speculated that the increased IgE and IL-4 in PCE-exposed workers could potentially contribute to allergic reactions of unknown etiology.

In another group of dry cleaning workers exposed to PCE on average for 1.5 years (blood PCE concentration =  $561 \pm 75$  ng/mL) compared to unexposed workers (blood PCE

---

<sup>45</sup> Dr. Gilbert acknowledged that mouse models, since they recapitulate human systems very well, are often used to estimate the effects of toxicants on human health. Gilbert Bladder Cancer Report, p. 9.

<sup>46</sup> Dr. Gilbert opines that PCE immunotoxicity, in combination with TCE and other VOCs, can promote bladder cancer development. Gilbert Bladder Cancer Report, p. 20-25. I note that Dr. Gilbert's analysis underlying this opinion is surprisingly brief as it consists of only six lines for human studies and six lines for animal studies on page 22 of her report.

concentration =  $1.3 \pm 0.5$  ng/mL), Li et al. (2024) reported significant increases in plasma concentrations of IL-1 $\beta$  and TNF- $\alpha$ , significant decreases in IL-2 and IL-8, and no effect on IFN- $\gamma$ , IL-4 or IL-6 in the PCE-exposed workers. The changes in plasma cytokine levels were accompanied by increased levels of antioxidant enzymes (i.e., superoxide dismutase-SOD, catalase-CAT, and malondialdehyde-MDA). The authors of this study concluded that plasma cytokines may be sensitive to PCE exposure.

Another investigation of immunological parameters was performed in a group of dry-cleaning workers exposed to PCE (Andrys et al., 1997). External exposure to PCE was reported as (8h)TWA<sup>47</sup> values in the range 11 – 752 mg/m<sup>3</sup>. End of shift biological monitoring showed PCE in exhaled breath in the range 9 – 344 mg/m<sup>3</sup>. In comparison to an unexposed control group, the PCE-exposed dry-cleaning workers had statistically significant increases in metabolic activity of phagocytes, serum  $\alpha$ 2-macroglobulin, C3 and C4 components of complement, secretory IgA (sIgA), and blast transformation responsiveness to T/B cell mitogen. Despite these statistically significant changes in various markers of innate and adaptive immunity, the authors acknowledged that the results, irrespective of PCE exposure, were within long-term laboratory reference values indicating that the data could be explained by normal individual variation in immune reactivity.

In a study examining maternal exposure to 28 different indoor VOCs including TCE and PCE, Lehmann et al., (2002) reported statistically significant decreased percentages of T cells producing several cytokines (i.e., IL-2, IL-4, TNF- $\alpha$ , and IFN- $\gamma$ ) in the umbilical cord blood of newborns from homes with higher levels of PCE ( $> 7.3$   $\mu$ g/m<sup>3</sup>, the 75<sup>th</sup> percentile concentration) compared with subjects from homes with lower levels of PCE, but not necessarily indeterminant levels of other VOCs. For homes with higher levels of TCE ( $> 1.0$   $\mu$ g/m<sup>3</sup>, the 75<sup>th</sup> percentile concentration), but not necessarily indeterminant levels of other VOCs, only the percentages of cord blood-derived T cells producing IL-2 were decreased in comparison to results from subjects from homes with lower levels of TCE, but not necessarily indeterminant levels of other VOCs. The authors correlated their findings on VOC exposures producing decreased T cell IFN- $\gamma$  production with family history of atopy—the predisposition to produce IgE and develop allergic reactions or asthma. The findings from this study have numerous limitations including potential confounding by co-exposure to multiple VOCs and failure to account for changes in indoor VOC concentrations over time.

As mentioned above, the available data on the immunotoxicity of PCE in humans do not provide a coherent picture concerning potential effects of PCE exposure on health

---

<sup>47</sup> An 8-hour time-weighted average (TWA) – the average exposure to a potentially harmful substance over an 8-hour work shift.

outcomes being attributable to immunomodulatory mechanisms. Moreover, the studies discussed above that examined associations between PCE exposure and various cytokines show, for the most part, inconsistent outcomes (Table 2). Consistency and coherence are both Bradford Hill Criteria, neither of which are met in considering PCE immunotoxicity as being operant in any human disease—including bladder cancer.<sup>48</sup>

**Table 2. Summary of Human Studies Reporting Effects of PCE on Cytokines.**

	IL-1 $\beta$	IL-2	IL-4	IL-6	IL-8	IFN- $\gamma$	TNF- $\alpha$
Emara et al., 2010	ND	ND	↑	ND	ND	ND	ND
Li et al., 2024	↑	↓	none	none	↓	none	↑
Lehmann et al., 2002	ND	↓	none	ND	ND	↓	↓
ND = not determined; none = no effect of PCE relative to control; ↑ = increase for PCE relative to control; ↓ = decrease for PCE relative to control							

Few studies on PCE immunotoxicity have been conducted in animals. Most of the rodent studies show minimal effects of PCE on immunological parameters even at high exposures. For example, no effects on the antibody forming cell response or phagocytic activity of alveolar macrophages were observed in Sprague Dawley rats exposed to PCE via inhalation at concentrations up to 1,000 ppm for 6 hours per day for 20 days (Boverhof et al., 2013).

In another study with Sprague Dawley rats and B6C3F1 mice exposed to PCE by intraperitoneal injection, despite the high dose exposure, no effects on splenic or hepatic NK cell cytotoxicity or lymphocyte responses to B cell and T cell mitogens were observed (Schlichting et al., 1992).

Significant increases in susceptibility to respiratory streptococcus infection were observed in mice exposed to 50 ppm PCE for 3 hours (Aranyi et al., 1986). Of note, interpretation of this study is complicated by the fact that the controls for one of the treated groups of mice had a higher mortality rate than any other group in the study (ATSDR, 2019b).

Finally, two reports by Seo et al., (2008a; 2008b) showed that exposure of Wistar rats to PCE via drinking water (0.01 – 1.0 mg/L for 2 to 4 weeks) enhanced immune effector

---

<sup>48</sup> I note that Dr. Gilbert indicated that she followed a modified Bradford Hill approach to derive her opinions. Gilbert Bladder Cancer Report, p. 7. However, this does not appear to be the case regarding the basis of her opinion concerning PCE immunotoxicity promoting bladder cancer development.

functions (e.g., mast cell histamine release, passive cutaneous anaphylaxis reaction, IL-4 expression) and increased activities of Th2-type CD4+ helper T cells. Similar experiments showed the same outcomes in mice exposed to PCE (Seo et al., 2012). These were studies that examined effects of PCE exposure on allergic responses. As such, the experimental designs and findings of these studies are not generalizable to informing anything of relevance concerning the immunobiology of bladder cancer. **It cannot be concluded that any of the apparent immunomodulatory effects of PCE exposure in rodents are operant etiologically in human bladder cancer. Therefore, both the animal and human studies discussed above do not support a plausible mechanistic pathway by which PCE could cause bladder cancer.**

### ***6.6.3 Benzene Immunotoxicity<sup>49</sup>***

Benzene, at high doses, is a known human hematotoxin (Goldstein, 1977). The highly reactive metabolites of benzene have long been known to affect hematopoiesis (i.e., the process by which blood cells are formed in the body. (Wang et al., 2012). The health effects of benzene have been studied extensively in humans and laboratory animals (ATSDR, 2024b). These studies establish that the primary target for benzene toxicity is the hematopoietic tissues. By disrupting hematopoiesis, benzene exposure can lead to decreased numbers of all lymphoid (e.g., B cells, T cells, etc.) and myeloid (e.g., neutrophils, monocytes, mast cells, etc.) cell lineages. By decreasing the numbers of these cells through the disruption of hematopoiesis, benzene can cause immunosuppression of both adaptive and innate immunity.<sup>50</sup> But the relevance of these studies to human bladder cancer can only be speculated.

---

<sup>49</sup> Dr. Gilbert opines that benzene immunotoxicity, in combination with TCE and other VOCs, can promote {bladder} cancer development. Gilbert Bladder Cancer Report, p. 20-25. I note that Dr. Gilbert's analysis underlying this opinion consists of five lines for human studies and three lines for animal studies on page 22 of her report. Dr. Gilbert provided no analysis supporting that the levels of exposure to benzene at or from Camp Lejeune were sufficient to cause hematotoxicity.

<sup>50</sup> Early experiments in mice showed that short-term (i.e., 6 days for 6 hours per day) inhalation exposures to benzene concentrations ranging between 10 to 300 ppm suppressed mitogenic responses of B and T lymphocytes (Rozen et al., 1984). Another study following a similar exposure paradigm showed that benzene inhalation reduced protective cell-mediated immune responses to sublethal challenge with the bacterium *Listeria monocytogenes* (Rosenthal & Snyder, 1985). Decreased splenic lymphocyte antibody production was observed in mice exposed by inhalation to benzene (50, 200 ppm - 6 hours/day for 7 days) (Aoyama, 1986). Inhalation exposure also was shown to inhibit cell mediated tumor surveillance (i.e., cytotoxic T cell function) in mice (Rosenthal & Snyder, 1987),

Effects of benzene on immune parameters have been studied in occupational cohorts. For example, in a study comprised of 250 benzene-exposed shoe workers, Lan et al., 2004 aimed at assessing benzene hematotoxicity at lower occupational exposure levels. The experimental design entailed stratifying the benzene workers into groups based on their exposure levels (i.e., <0.04 ppm, < 1 ppm, 1 to 10 ppm, and > 10 ppm), and then assessing cell counts in peripheral blood for CD4+ cells, CD8+ cells, B cells, and NK cells. Modest, but statistically significant, decreases in the numbers of these cell populations were found in some of the benzene-exposed workers relative to the control population (i.e., < 0.04 ppm benzene). Although the data appear to show statistically significant lower cell counts for all lymphocyte subsets in benzene-exposed groups relative to the control group, there was no functional immunosuppression assessed in this study. Irrespective of the statistical differences, no functional immunosuppression would be expected based on the findings because the data establish that the vast majority of the subjects in this study across the exposure groups, ranging from control to the various benzene exposures, fall within *normal* counts for each of the lymphocyte subpopulations tabulated. Thus, contrary to the interpretation of the authors, the Lan (2004) study data show that the immune systems of these benzene-exposed subjects were normal with respect to peripheral blood lymphocyte subset counts. The data support that the vast majority of the subjects in this study, irrespective of their benzene exposure, are immunocompetent (i.e., have lymphocyte subset counts within normal ranges)—not immunodeficient or immunosuppressed. **As such, these findings do not support a conceptual framework that benzene causes immunosuppression as a mechanism contributing to the etiology of bladder cancer.**

Some animal studies show that benzene exposure has different effects, depending on dose or its combination with toluene. For example, exposure to benzene via the drinking water (i.e., 31, 166, 790 mg/L for 4 weeks) in mice produced dose-related biphasic responses for B and T cell mitogens, cell-mediated immunity, splenic antibody formation, and cytotoxic T cell activity. The immune responses were *enhanced* at low levels of benzene exposure and *suppressed* at higher doses (Hsieh et al., 1988). A follow-up study in which benzene and toluene were co-administered showed that toluene completely *inhibited* the immunosuppressive effects of benzene when co-administered with benzene (Hsieh et al., 1990).

Generally speaking, plaintiffs' experts take the position that exposures to benzene produce harmful toxic effects that can contribute to bladder cancer through vaguely described mechanisms.<sup>51</sup> As discussed in Section 6.1.3, different metabolites are produced

---

<sup>51</sup> Bird Bladder Cancer Report, p. 18-19; Plunkett Bladder Cancer Report, p. 30-31; Hatten Bladder Cancer Report, p. 14, 29-30.



depending on the metabolic pathway, and those various metabolites are target-organ specific. This means that a chemical, such as benzene, that primarily affects the hematopoietic tissues, may have little or no effect on the bladder. Moreover, in apparent support of her implication of benzene in the etiology of bladder cancer, Dr. Gilbert cited to a review by Guo et al. (2021). Dr. Gilbert failed to acknowledge that this review promulgates various possibilities regarding how benzene might facilitate carcinogenesis, without citing definitive scientific evidence to support that the possible effects are correct. Thus, the Guo review cannot support a conclusion that benzene exposure contributes to bladder tumor progression or regression through pro-inflammatory or immunosuppressive mechanisms.

#### ***6.6.4 Vinyl Chloride Immunotoxicity<sup>52</sup>***

The peer-reviewed scientific literature concerning potential effects of vinyl chloride on the immune system or inflammatory processes is not extensive. Therefore, the limited number of studies and adequacy of the data are not generalizable to the immunobiology of bladder cancer and cannot inform that vinyl chloride contributes causatively to bladder cancer through immunotoxic mechanisms.

Some workers exposed to high levels of vinyl chloride by inhalation develop a rare syndrome called “vinyl chloride disease,” characterized by Raynaud’s phenomenon (feelings of numbness and cold in fingers and toes), acro-osteolysis (dissolution of the bones of the terminal phalanges and sacroiliac joints) and scleroderma-like skin changes (tightness, thickening, hardening of the skin). Features of vinyl chloride disease include the presence of high levels of circulating immune complexes, elevated pro-inflammatory cytokines (i.e., TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-8), increased serum immunoglobulins (i.e., IgG, IgM, IgA), and increased activities of complement and acute phase reactive components (ATSDR, 2024). Vinyl chloride disease exhibits characteristics of an autoimmune disease, whereby reactive intermediates of VC metabolism may produce changes in self-proteins (i.e., neoantigens) that are recognized by the immune system thereby stimulating effector functions (e.g., pro-inflammatory cytokine release, complement activation) that mediate the pathological changes observed. The probable triggering events that lead to autoimmune vinyl chloride disease are not readily generalizable to bladder cancer initiation. No studies have reported the formation of unique tumor antigens in the bladders of subjects exposed to vinyl chloride—or for any other VOCs.

---

<sup>52</sup> Dr. Gilbert’s opinion concerning cumulative co-exposures to VOCs at or from Camp Lejeune did not include consideration that vinyl chloride immunotoxicity contributed to bladder cancer. See Gilbert Bladder Cancer Report. Her report did not include any analysis concerning vinyl chloride immunotoxicity.



The immunological effects of vinyl chloride exposure also were examined through animal studies in mice and rabbits (Sharma & Gehring, 1979; Sharma et al., 1980). These studies showed that lymphocyte responses to mitogens were increased for mice and rabbits exposed to VC via inhalation at 10, 1000, 1000 ppm for 6 hours per day, 5 days per week, for 2 to 4 weeks. Although vinyl chloride appeared to be immunostimulatory in these studies, it was shown not to affect antigen-specific responses (i.e., it was not generally immunotoxic). The authors speculated that the immunostimulatory effects of vinyl chloride seen in mice and rabbits were somehow consistent with the reported involvement of vinyl chloride in human immune complex disorders. This is an interpretive leap that is unfounded.

Therefore, the animal and human studies do not show a plausible mechanistic pathway by which vinyl chloride could cause bladder cancer.

## **7.0 CRITIQUE OF PLAINTIFFS' EXPERT'S GENERAL CAUSATION OPINIONS**

In order to render an opinion on whether immunological effects of TCE, PCE, benzene, and vinyl chloride can cause bladder cancer, a scientist must perform a critical assessment of all of the available and relevant human and scientific studies that may provide information relevant to the question. Plaintiffs' experts who have referenced immunological effects of these chemicals and linked them to bladder cancer have failed to do this. In some instances, they have not reviewed certain literature, at all. In other instances, they have not critically assessed the literature cited in support of opinions, when a critical evaluation shows that it does not support their conclusions.

In her General Causation Report on TCE and Bladder Cancer, Dr. Gilbert, plaintiffs' only immunologist, proffered five opinions. I will address the opinions that suggest immunotoxicity is implicated in bladder cancer.

In her Opinion 2, Dr. Gilbert opines that TCE, PCE and benzene causes immunotoxicity that can promote bladder cancer development. Dr. Gilbert suggests that TCE, PCE and benzene are immunotoxic thereby causing bladder cancer, since the immune system and inflammatory processes are important in bladder cancer. However, Dr. Gilbert failed to acknowledge that no national or international regulatory agencies have concluded that immunomodulation is operant as a mode of action for TCE-induced bladder cancer<sup>53</sup>, nor

---

<sup>53</sup> In her report, Dr. Gilbert cites to the USEPA Risk Evaluation of Trichloroethylene (2020), wherein it states that "overall, immunotoxicity in the form of both autoimmunity and immunosuppression following TCE exposure are supported by the weight of evidence." Gilbert Bladder Cancer Report, p. 25. However, this document did not conclude that the weight of the evidence linked these mechanisms causatively to

have any national or international regulatory agencies taken the position that PCE or benzene immunotoxicity are linked causatively to bladder cancer. Moreover, Dr. Gilbert failed to acknowledge or consider that there are no on-point experimental studies in mouse or man published in the peer-reviewed scientific literature showing that TCE, PCE or benzene play any role in bladder tumor progression or regression through immune mechanisms.

The basis of Dr. Gilbert's unique opinion that TCE and PCE induce immune dysfunction and chronic inflammation leading to bladder cancer is summarized in Figure 3 of her report.<sup>54</sup> The figure is entitled "Model for TCE and/or PCE-induced bladder cancer."<sup>55</sup> The content of this figure does not establish that TCE and/or PCE cause bladder cancer through mechanisms that involve immune dysfunction or chronic inflammation. In my view, the figure sets forth nothing more than a conceptual framework for hypotheses that could be tested. For example, there is no direct evidence that TCE or PCE disrupt cancer immunoediting leading to bladder cancer by any of the posited immune dysfunctions depicted. The notion that immunosuppression disrupts cancer immunosurveillance, which again is only a hypothesis, is undermined by my analysis (Section 6.6.1) detailing that statistical associations (e.g., decreased lymphocyte counts and immunoglobulin levels) do not evidence functional immunosuppression in humans. If the hypothesis is undermined, then the conclusion is not valid.

Figure 3 of Dr. Gilbert's report also proposes the hypothesis that chronic inflammation, triggered by TCE and PCE, causes bladder cancer. Inflammation is ubiquitous—it is caused by many extrinsic factors and intrinsic processes (Singh et al., 2019). As mentioned earlier in this report there is the notion of "good" inflammation, which a component of immune protection, and there is "bad" inflammation, which has been implicated in the pathogenesis of nearly every chronic disease ranging from A to Z (e.g., from atherosclerosis to Zellweger syndrome). Given the ubiquity of inflammatory processes in many multifactorial complex diseases, including bladder cancer, assigning a causal inference to any particular intrinsic or extrinsic factor, including TCE or PCE, as a pathogenic mechanism in any disease is highly speculative. Chronic inflammation is a characteristic of bladder cancer, especially as the tumor progresses, and it occurs *without* TCE or PCE exposure. This begs the question - how does Dr. Gilbert propose that chronic inflammation in bladder cancer differs between those who are TCE-exposed, or PCE-exposed, or benzene-exposed versus those who are not? In other words, how do inflammatory mechanisms hypothetically triggered by TCE, PCE or benzene differ from "background" inflammation that

---

bladder cancer.

<sup>54</sup> Gilbert Bladder Cancer Report, p. 25 (listed in same as Figure 1).

<sup>55</sup> I note the absence of benzene in Dr. Gilbert's model of bladder cancer causation. See Gilbert Bladder Cancer Report.

is inherent to the disease? There are no experimental studies in the scientific literature that test these issues separately to answer these questions. There is no scientific basis (i.e., data) supporting that TCE, PCE or benzene tip the balance toward harmful inflammation. As such, the connection made by Dr. Gilbert between TCE-, PCE-, or benzene-induced chronic inflammation and bladder cancer is superficially hypothetical. It is untested and unproven.

In her Opinion 3, Dr. Gilbert opines that contaminant-induced oxidative stress can augment immunotoxicity in promoting bladder cancer. Dr. Gilbert notes that TCE, PCE and benzene can produce oxidative stress. Since oxidative stress appears to be important in bladder cancer etiology, Dr. Gilbert claims that oxidative stress induced by these toxicants is a mechanism whereby they cause bladder cancer. The generation of reactive oxygen species (ROS) occurs extensively in normal cells, and the potential for damage is held in check by antioxidants that are important for maintaining homeostasis within the body. When the generation of ROS species exceeds antioxidant defenses, the resulting imbalance is called oxidative stress. Oxidative stress is a catch-all description for a multitude of redox reactions that can become imbalanced resulting in oxidative damage to various cellular constituents. Oxidative stress can be triggered by endogenous factors (e.g., free radicals generated as byproducts of oxygen metabolism) or by numerous exogenous factors (e.g., viruses). Oxidative stress is linked mechanistically to various outcomes including changes in gene expression, genotoxicity, cell cytotoxicity, and inflammation. Dr. Gilbert acknowledges that oxidative stress can either be causal or secondary to inflammation<sup>56</sup>, which is true. However, she failed to define if the oxidative stress purportedly caused by TCE, PCE, or benzene was causal or secondary to inflammation, and she failed to explain how causal versus secondary oxidative stress attributable to TCE, PCE, or benzene could be determined.

Dr. Gilbert fails to acknowledge the ubiquity of reactive oxygen species in normal cellular processes as well as in disease. As was the case with the basis of her opinion concerning inflammatory processes, Dr. Gilbert would be hard-pressed to separate out TCE-induced oxidative stress from "background" oxidative stress that is inherent to a chronic disease process like bladder cancer. Oxidative stress is ubiquitous as a pathogenic mechanism in many chronic diseases. As such, Dr. Gilbert's opinion that TCE-induced oxidative stress can cause bladder cancer is built on generalities. Her analysis does not inform that TCE exposure at levels found at Camp Lejeune causes more oxidative stress in TCE-exposed subjects or triggers more antioxidant defenses than occur in the absence of

---

<sup>56</sup> Gilbert Bladder Cancer Report, p. 19.

TCE exposure. Observations of a role for TCE-induced oxidative stress as a mechanism of disease in particular autoimmune prone mice (Khan & Wang, 2018; Wang et al., 2007) are not generalizable for informing that TCE-induced oxidative stress is operant as a mechanism in causing bladder cancer in humans.

In her Opinion 4, Dr. Gilbert opines that levels of TCE and other VOCs at Camp Lejeune were hazardous to human health. Other experts have been tasked with addressing Dr. Gilbert's fourth opinion (i.e., Drs. Goodman, Shields, etc.). However, I note the striking absence of any attempt by Dr. Gilbert to link her fourth opinion to her second and third opinions. That is to say, Dr. Gilbert failed to demonstrate that the mechanisms that she proposes cause bladder cancer occur at environmentally relevant exposures to TCE, PCE, and benzene<sup>57</sup> specific to Camp Lejeune. As detailed in my analysis in Section 6.6.1 of this report, some statistically significant, but functionally irrelevant, effects of TCE have been found in cross-sectional study designs in subjects exposed occupationally to high concentrations of TCE. Some animal studies show that immunomodulation—either immune suppression or immune stimulation—occurs in rodents typically dosed with very high concentrations of TCE, and the immune pathologies observed are separate and apart from bladder cancer. Also, in Sections 6.6.2 and 6.6.3, I discuss how the state of knowledge concerning PCE and benzene immunotoxicity, respectively, are insufficient to implicate them in the etiology of bladder cancer. Collectively, these human and animal studies do not establish that TCE, alone or in combination with PCE or benzene, modulates the immune system at levels of exposure that are relevant to purported Camp Lejeune exposures. As such, they do not inform that the levels of exposure to TCE at Camp Lejeune caused bladder cancer by affecting the immune system or inflammatory processes.

In her Opinion 5, Dr. Gilbert opines that the likelihood that the VOCs in the drinking water at Camp Lejeune caused bladder cancer was increased by aggregate exposure via inhalation and dermal routes, and by cumulative co-exposure. Other experts have been tasked with addressing Dr. Gilbert's fifth opinion (i.e., Dr. John Lipscomb, etc.). I note, however, as was the case with Dr. Gilbert's fourth opinion, Dr. Gilbert's fifth opinion is not linked to her second and third opinions. That is, Dr. Gilbert failed to demonstrate that the postulated, but unquantified, cumulative effects of co-exposure to TCE, PCE and benzene caused bladder cancer through their additive effects on the immune system, inflammatory processes or oxidative stress. In fact, Dr. Gilbert's analysis is largely disputed by my own analysis concerning potential effects of PCE and benzene individually on these mechanisms.

---

<sup>57</sup> Vinyl chloride is not a chemical discussed in Dr. Gilbert's report. See Gilbert Bladder Cancer Report.

Finally, other plaintiffs' experts (e.g., Dr. Laura M. Plunkett and Dr. Steven B. Bird), neither of whom are immunologists, opined superficially that there is an intersection between Camp Lejeune VOCs, immunotoxicity, and bladder cancer etiology in their respective reports. Their analyses were not sufficiently detailed to reliably support the opinions they asserted. Drs. Bird and Plunkett fail to critically analyze the data and experimental studies concerning TCE, PCE, benzene, and vinyl chloride, with respect to their posited effects on the immune system and inflammatory responses. Their comments on the potential immunotoxicity of Camp Lejeune VOCs do little to advance plaintiffs' arguments that altered immunity by these chemicals is involved in the etiology of bladder cancer.

## **8.0 FINDINGS AND OPINIONS**

There is scientific literature concerning the immunotoxicity of TCE in animals and, to a lesser extent, humans. None of the animal studies or human observations concerning TCE and the immune system have been done or made within the contexture of any cancer—including bladder cancer. There is little doubt that the tumor microenvironment in bladder cancer can be shaped by immune and inflammatory processes, which under various circumstances can either have a positive effect (i.e., anti-tumor) or, conversely, an unfavorable outcome (i.e., tumor progression leading to clinical disease). In short, the intersection between the immune system and the etiology of bladder cancer is complex. This inherent complexity in the immunobiology of bladder cancer, with its associated variability, makes drawing any conclusions about potential immunotoxic contributions to bladder cancer causation in the absence of direct experimental proof fraught with problems requiring scientifically unmeritorious leaps in logic.

At best, the existing literature concerning TCE immunotoxicity provides a conceptual framework (i.e., background) for formulating a hypothesis that TCE causes bladder cancer through mechanisms that involve perturbations of the immune response or inflammatory processes. Intellectually honest scientists can debate whether such a hypothesis is sufficiently compelling enough to warrant experimental testing aimed at obtaining findings that support or refute the proposition that myriad effects of TCE on the immune system mechanistically cause bladder cancer. However, leapfrogging over the necessity to test by adopting the mere hypothesis, itself, as being conclusive belies the sanctity of the Scientific Method.

Based on the foregoing, my professional opinions, all of which I hold to a reasonable degree of scientific certainty are as follows:

Opinion 1: My independent analysis demonstrates that relevant animal and human studies do not show that modulation of the immune system is a plausible mechanistic pathway by which TCE, PCE, benzene, and vinyl chloride cause bladder cancer.

Opinion 2: Plaintiffs' expert, Dr. Kathleen Gilbert, has opined that TCE, PCE and benzene "causes immunotoxicity that can promote cancer development." It is my opinion that Dr. Gilbert's novel opinion is without support and is merely a hypothesis that heretofore has not been adequately tested. The existing data and available scientific studies do not show that perturbations of the immune system or inflammatory processes by TCE, PCE and benzene, alone or in combination, are operant mechanistically as causes of bladder cancer. Leapfrogging over the necessity to test – a fundamental aspect of the scientific method – by adopting the mere hypothesis itself as conclusive, as Dr. Gilbert does, belies the purpose of engaging in the scientific method.

Opinion 3: Other plaintiffs' experts (e.g., Dr. Laura M. Plunkett and Dr. Steven B. Bird), neither of whom are immunologists, opined superficially that there is an intersection between Camp Lejeune VOCs, immunotoxicity and bladder cancer etiology in their respective reports. Their analyses were not sufficiently detailed to reliably support the opinions asserted. They fail to critically analyze the data and experimental studies concerning TCE, PCE, benzene, and vinyl chloride, with respect to their posited effects on the immune system and inflammatory processes. The relevant studies show no effects on the immune system and inflammatory processes that could support plaintiffs' experts' opinions that TCE, PCE, benzene, and vinyl chloride can cause bladder cancer.

I reserve the right to supplement the basis or modify these opinions should additional information be made available to me.

## **9.0 COMPENSATION**

Currently, since April 2024, I am employed as a Principal Scientist by Intertox, Inc. I am a salaried employee and have no ownership interest in Intertox. As such, my compensation is not directly tied to time invoiced for my work on this case. The hourly rate for my work on the Camp Lejeune cases is \$575.

## **10.0 EXHIBITS TO TESTIMONY**

As exhibits to illustrate my testimony, I may use any or all documents referenced in this report, any or all documents and materials referenced at the end or footnoted in this report, and any and all material referenced in plaintiffs' expert reports.

## **11.0 CASE-SPECIFIC DOCUMENTS REVIEWED**

1. Plaintiffs' Master Complaint No. 7:23-CV-897
2. United States' Answer to the Master Complaint
3. Notice of Submission by the Plaintiff Leadership Group Regarding Disease Counts
4. Scheduling Order
5. Expert Report of Remy J.-C. Hennet, December 9, 2024
6. Expert Report of Alexandros Spiliotopoulos, December 9, 2024
7. Expert Report of Jay L. Brigham, December 9, 2024
8. Expert Report of Jay L. Brigham, February 7, 2025
9. Expert Report of Ari Kelman, February 7, 2025
10. Expert Report of Peter G. Shields, February 7, 2025
11. Expert Report on Bladder Cancer of Julie E. Goodman, February 7, 2025
12. Expert Report on Kidney Cancer of Julie E. Goodman, February 7, 2025
13. Expert Report on Non-Hodgkin's Lymphoma of Julie E. Goodman, February 7, 2025
14. Expert Report on Leukemia of Julie E. Goodman, February 7, 2025.
15. Expert Report on Parkinson's Disease of Julie E. Goodman, February 7, 2025
16. Expert Report of John C. Lipscomb, February 7, 2025
17. Expert Report of Morris L. Maslia, October 25, 2024
18. Expert Report of Mustafa M. Aral, October 25, 2024
19. Expert Report of Norman L. Jones and R. Jeffery Davis, October 25, 2024
20. Rebuttal Expert Report of Leonard F. Konikow, January 14, 2025
21. Rebuttal Expert Report of Kyle Longley, January 14, 2025
22. Rebuttal Expert Report of David Sabatini, January 14, 2025
23. Rebuttal Expert Report of Norman L. Jones and R. Jeffery Davis, January 14, 2025
24. Rebuttal Expert Report of Morris L. Maslia, January 14, 2025
25. Expert Report on Kidney Cancer of Dr. Steven B. Bird, December 5, 2024.
26. Expert Report on Kidney Cancer of Dr. Michael D. Freeman, December 5, 2024.
27. Expert Report on Kidney Cancer of Dr. Kathleen M. Gilbert, December 5, 2024.
28. Expert Report on Kidney Cancer of Dr. Benjamin Hatten, December 5, 2024.
29. Expert Report on Kidney Cancer of Dr. Timothy Mallon, December 5, 2024.
30. Expert Report on Bladder Cancer of Dr. Steven B. Bird, December 5, 2024.
31. Expert Report on Bladder Cancer of Dr. Stephen H. Culp, December 5, 2024.
32. Expert Report on Bladder Cancer of Dr. Kathleen Gilbert, December 5, 2024.
33. Expert Report on Bladder Cancer of Dr. Benjamin Hatten, December 5, 2024.
34. Expert Report on Bladder Cancer of Dr. Laura Plunkett, December 5, 2024.
35. Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Steven B. Bird, December 5, 2024.



36. Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Dean W. Felsher, December 5, 2024.
37. Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Kathleen Gilbert, December 5, 2024
38. Expert Report on Leukemia of Dr. Lukasz P. Gondek, December 5, 2024
39. Expert Report on Leukemia of Dr. Timothy M. Mallon, December 5, 2024
40. Expert Report on Non-Hodgkin Lymphoma of Dr. Howard Hu, December 5, 2024
41. Expert Report on Parkinson's Disease of Dr. Steven B. Bird, December 5, 2024
42. Expert Report on Parkinson's Disease of Dr. Amelia K. Boehme, December 5, 2024
43. Expert Report on Parkinson's Disease of Dr. Jason Cannon, December 5, 2024
44. Expert Report on Parkinson's Disease of Dr. Lucio Costa, December 5, 2024
45. Expert Report on Parkinson's Disease of Dr. Briana DeMiranda, December 5, 2024
46. Expert Report on Parkinson's Disease of Dr. Michael Freeman, December 5, 2024
47. Expert Report on Parkinson's Disease of Dr. Gary Miller, December 5, 2024
48. Expert Report of Kyle Longley, December 5, 2024
49. Supplemental Report of Dr. Jason Cannon, January 10, 2025
50. Supplemental Report of Dr. Howard Hu, January 31, 2025
51. Bove, FJ. "Videotaped & videoconferenced deposition of Dr. Frank J. Bove [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, October 17, 18, 2024
52. Savitz, DA. "Videotaped & videoconferenced deposition of Dr. David A. Savitz [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, June 10, July 17, 2024
53. Maslia, M. "Videotaped & videoconferenced deposition of Morris Maslia [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, September 26, 2024
54. Martel, SNJ. "Videotaped & videoconferenced deposition of Susan N.J. Martel [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, September 26, 2024
55. Agency for Toxic Substances and Disease Registry (ATSDR). 2017a. "Public Health Assessment Camp Lejeune Drinking Water, U.S. Marine Corps Base Camp Lejeune, North Carolina." January 20, 2017.
56. 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.

57. Agency for Toxic Substances and Disease Registry (ATSDR). 2007. "Analyses of Groundwater Flow, Contaminant Fate and Transport, and Distribution of Drinking Water at Tarawa Terrace and Vicinity, U.S. Marine Corps Base Camp Lejeune, North Carolina: Historical Reconstruction and Present-Day Conditions: Chapter A." July 2007.
58. Agency for Toxic Substances and Disease Registry (ATSDR). 2013. "Analyses and Historical Reconstruction of Groundwater Flow, Contaminant Fate and Transport, and Distribution of Drinking Water Within the Service Areas of the Hadnot Point and Holcomb Boulevard Water Treatment Plants and Vicinities, U.S. Marine Corps Base Camp Lejeune, North Carolina: Chapter A." May 2013.
59. Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC. 2014a. "Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study." *Environ. Health* 13:68. doi: 10.1186/1476-069X-13-68.
60. Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC. 2014b. "Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study." *Environ. Health* 13:10. doi:10.1186/1476-069X-13-10.
61. Agency for Toxic Substances and Disease Registry (ATSDR). 2018. "Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune." April 2018.
62. Bove, FJ; Greek, A; Gatiba, R; Boehm, RC; Mohnsen, MM. 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* 23(1):61. doi: 10.1186/s12940-024-01099-7.
63. Bove, FJ. 2024b. "Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: A cohort study." *Res. Square* doi: 10.21203/rs.3.rs-4171975/v1.
64. Bove, FJ; Greek A; Gatiba, R; Kohler, B; Sherman, R; Shin, GT; Bernstein, A. 2024c. "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.* 132(10):107008. doi: 10.1289/EHP14966.
65. National Research Council (NRC). 2009. "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects." National Academies Press, Washington, DC. 2009.
66. Rosenfeld PE, Spaeth KR, McCarthy SJ, Winter SC, Wilson MS, Hagemann M. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955 to 1987. *Water, Air, & Soil Pollution* 2024; 235: 124.
67. Rosenfeld PE, Spaeth KR, McCarthy SJ, Winter SC, Wilson MS. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955-

1987 (PrePrint). <https://ssrn.com/abstract=4329666>.  
68. CLJA\_RosenfeldSubpoena\_0000000001

## 12.0 LITERATURE RESOURCES REVIEWED, CONSIDERED AND RELIED UPON

Adami HO, Berry CL, Breckenridge CB, Smith LL. 2011. Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. *Toxicol Appl Pharmacol* 122:223-234.

Anders MW, Lash L, Dekant W, et al. 1988. Biosynthesis and biotransformation of glutathione S-conjugates to toxic metabolites. *CRC Crit Rev Toxicol* 18:311-341.

Andrys C, Hanovcova I, Chylkova V, Tejral J, et al. 1997. Immunological monitoring of dry-cleaning shop workers – exposure to tetrachloroethylene. *Centr Eur J Publ Hlth* 5:135-142.

Aoyama K. 1986. Effects of benzene inhalation on lymphocyte subpopulations and immune response in mice. *Toxicol Appl Pharmacol* 85:92-101.

Apoil PA, Puissant-Lubrano B, Congy-Jolivet N, Pere M, et al. 2017. Reference values for T, B and NK human lymphocytes subpopulations in adults. *Data in Brief* 12:400-404.

Aranyi C, O'Shea WJ, Graham JA, Miller FJ. The effects of inhalation of organic chemical air contaminants on murine lung host defenses. *Fundam Appl Toxicol*. 1986 May;6(4):713-20.

ATSDR. 2019. Toxicological Profile for Trichloroethylene. US Department of Health and Human Services Public Health Service.

ATSDR. 2019b. Toxicological Profile for Tetrachloroethylene. US Department of Health and Human Services Public Health Service.

ATSDR. 2024. Toxicological Profile for Vinyl Chloride. US Department of Health and Human Services Public Health Service.

ATSDR. 2024b. Toxicological Profile for Benzene. US Department of Health and Human Services Public Health Service.

Banerjee N, Wang H, Wang G, Khan MF. 2020. Enhancing the Nrf2 Antioxidant Signaling Provides Protection Against Trichloroethene-mediated Inflammation and Autoimmune Response. *Toxicol Sci* 175:64-74.

Bassig BA, Zhang L, Vermeulen R, Tang X, et al. 2016. Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene. *Carcinogenesis* 37:692-700.

Bassig BA, Zhang L, Tang X, Vermeulen R, et al. 2013. Occupational exposure to trichloroethylene and serum concentrations of IL-6, IL-10, and TNF-alpha. *Environ Mol Mutagen* 54:450-454.

Basu A, Ramamoorthi G, Albert G, Gallen C, et al. 2021. Differentiation and regulation of T<sub>H</sub> cells: a balancing act for cancer immunotherapy. *Front Immunol* 12:669474.

Birner G, Rutkowska A, Dekant W. 1996. N-Acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine and 2,2,2-trichloroethanol: Two novel metabolites of tetrachloroethene in humans after occupational exposure. *Drug Metab Dispos* 24(1):41-48.

Blossom SJ, Doss JC, Gilbert KM. 2006. Ability of trichloroethylene metabolite to promote immune pathology is strain specific. *J Immunotoxicol* 3:179-187.

Boivin-Angele S, Lefrancois L, Froment O, Spiethoff A, et al. 2000. Ras gene mutations in vinyl chloride-induced liver tumours are carcinogen-specific but vary with cell type and species. *Int J Cancer* 85:223-227.

Bolt HM, Kappus H, Buchter A, et al. 1976. Disposition of (1,2-<sup>14</sup>C) vinyl chloride in the rat. *Arch Toxicol* 35(3):153-162.

Boverhof DR. 2013. Assessment of the immunotoxic potential of trichloroethylene and perchloroethylene in rats following inhalation exposure. *J Immunotoxicol* 10:311-320.

Buben JA, O'Flaherty EJ. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose-effect study. *Toxicol Appl Pharmacol* 78:105-122.

Chen L, Lang AL, Poff GD, et al. 2019. Vinyl chloride-induced interaction of nonalcoholic and toxicant-associated steatohepatitis: Protection by the ALDH2 activator Alda-1. *Redox Biol* 24:101205.

Chiu WA, Ginsberg GL. 2011. Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans. *Toxicol Appl Pharmacol*. 2011 Jun 15;253(3):203-34.

Choudhury SR, Byrum SD, Blossom SJ. 2024. Trichloroethylene metabolite modulates DNA methylation-dependent gene expression in Th1-polarized CD4+ T cells in autoimmune prone mice. *Toxicol Sci* 199:289-300.

Cichocki JA, Guyton KZ, Guha N, Chiu WA, et al. Target organ metabolism, toxicity, and mechanisms of trichloroethylene and perchloroethylene: key similarities, differences, and data gaps. *J Pharmacol Exp Ther* 359:110-123.

Clemente CG, Mihm MC Jr, Bufalino R, Zurrida S, et al. 1996. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer* 77:1303-1310.

Cooper GS, Makris SL, Nietart PJ, Jinot J. 2009. Evidence of autoimmune-related effects of trichloroethylene exposure from studies in mice and humans. *Environ Health Perspect* 117:696-702.

Cui H, Wu J, Du G, Hu L, et al. 2024. Dynamic changes in serum immunoglobulin G predict

Dallas CE, Chen XM, Muralidhara S, et al. 1994a. Use of tissue disposition data from rats and dogs to determine species differences in input parameters for physiological model for perchloroethylene. *Environ Res* 67:54-67.

Dallas CE, Chen XM, O'Barr K, et al. 1994b. Development of a physiologically based pharmacokinetic model for perchloroethylene using tissue concentration - time data. *Toxicol Appl Pharmacol* 128:50-59.

Dati F, Schumann G, Thomas L, Aguzzi F, Baudner S. 1996. Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP Reference Material (CRM 470). International Federation of Clinical Chemistry. Community Bureau of Reference of the Commission of the European Communities. College of American Pathologists. *Eur J Clin Chem Clin Biochem* 34:517-520.

Desponds E, Kioseoglu K, Zdimerova H, Ongaro M, et al. 2024. Development of traceable mouse models of advanced and metastatic bladder cancer. *Cancers* 16:2245.

Dieu-Nosjean MC, Antoine M, Danel C, Heudes D, et al. 2008. Long-term survival for patients with non-small-cell lung cancer with intratumoral lymphoid structures. *J Clin Oncol* 26:4410-4417.

Doonan R, McElwee JJ, Matthijssens F, Walker GA, et al. 2008. Against the oxidative damage theory of aging: superoxide dismutases protect against oxidative stress but have little or no effect on life span in *Caenorhabditis elegans*. *Genes Dev* 22:3236-3241.

Dyrskot L, Hansel DE, Efsthathiou JA, Knowles MA, et al. 2023. Bladder cancer. *Nat Rev Dis Primers* 9:58.

Emara AM, Abo El-Noor MM, Hassan NA, Wagih AA. 2010. Immunotoxicity and hematotoxicity induced by tetrachloroethylene in Egyptian dry cleaning workers. *Inhal Toxicol* 22:117-124.

Fantini D, Glaser AP, Rimar KJ, Wang Y, et al. 2018. A carcinogen-induced mouse model recapitulates the molecular alterations of human muscle invasive bladder cancer. *Oncogene* 37:1911-1925.

Fedak KM, Bernal A, Capshaw ZA, Gross S. 2015. Applying the Bradford Hill Criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 12:14-22.

Finn OJ. 2018. A believer's overview of cancer immunosurveillance and immunotherapy. *J Immunol* 200:385-391.

Fridman WH, Mlecnik B, Bindea G, Pages F, Galon J. 2011. Immunosurveillance in human non-viral cancers. *Curr Opinion Immunol* 23:272-278.

Fridman WH, Pages F, Sautes-Fridman C, Galon J. 2012. The immune contexture in human tumours: impact on clinical outcome. *Nature* 12:298-306.

Fridman WH, Dieu-Nosjean MC, Pages F, Cremer I, et al. 2013. The immune microenvironment of human tumors: general significance and clinical impact. *Cancer Microenviron* 6:117-122.

Geginat J, Paroni M, Maglie S, Alfen JS, et al. 2014. Plasticity of human CD4 T cell subsets. *Front Immunol* 5:630.

Ghezzi P, Jaquet V, Marcucci F, Schmidt HHHW. 2017. The oxidative stress theory of disease: levels of evidence and epistemological aspects. *Br J Pharmacol* 2017 Jun;174(12):1784-1796.

Gilbert KM, Nelson AR, Cooney CA, Reisfeld B, Blossom SJ. 2012. Epigenetic alterations may regulate temporary reversal of CD4(+) T cell activation caused by trichloroethylene exposure *Toxicol Sci* 127:169-178.

Gilbert KM, Blossom SJ, Erickson SW, et al. 2016a, Chronic exposure to trichloroethylene increases DNA methylation of the ifng promoter in CD4(+) T cells. *Toxicol Lett* 260:1-7.

Gilbert KM, Blossom SJ, Erickson SW, et al. 2016b, Chronic exposure to water pollutant trichloroethylene increased epigenetic drift in CD4+ T cells. *Epigenomics* 8:633-649.

Gilbert KM. 2014. Chapter 22. Trichloroethylene and Autoimmunity in Human and Animal Models. In *Trichloroethylene: Toxicity and Health Risks*. Springer/Humana Press, New York/Heidelberg. Gilbert, K.M. and Blossom, S.J. (eds), 2014.

Goldstein BD. 1977. Hematotoxicity in humans. *J Toxicol Environ Health Suppl* 2:69-106.

Gonzalez H, Hagerling C, Werb Z. 2018. Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes Dev* 32:1267-1284.

Griffin JM, Blossom SJ, Jackson SK, Gilbert KM, Pumford NR. 2000. Trichloroethylene accelerates an autoimmune response by Th1 T cell activation in MRL +/+ mice. *Immunopharmacol* 46:123-37.

Guo H, Ahn S, Zhang L. 2021. Benzene-associated immunosuppression and chronic inflammation in humans: a systemic review. *Occ Environ Med* 78:377-384.

Hefner RE, Watanabe PG, Gehring PJ. 1975a. Percutaneous absorption of vinyl chloride. *Toxicol Appl Pharmacol* 34(3):529-532.

Hefner RE, Watanabe PG, Gehring PJ. 1975b. Preliminary studies on the fate of inhaled vinyl chloride monomer (VCM) in rats. *Environ Health Perspect* 11:85-95.

Henderson RF, Sabourin PJ, Bechtold WE, 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* 82:9-17.

Henderson RF. Species differences in the metabolism of benzene. *Environ Health Perspect.* 1996 Dec;104 Suppl 6(Suppl 6):1173-5

Hill AB 1965. The Environment and Disease: Association or Causation? *Proc Roy Soc Med* 58:295-300.

Hosgood HD, Zhang, L, Tang X, Vermeulen R. 2012. Decreased numbers of CD4+ naïve and effector memory cells, and CD8+ naïve T cells, are associated with trichloroethylene exposure. *Front Oncol* 1:1-6.

Hsieh GC, Sharma RP, Parker RD. 1988. Subclinical effects of groundwater contaminants 1: alterations of humoral and cellular immunity by benzene in CD-1 mice. *Arch Environ Contam Toxicol* 17:151-158.



Hsieh GC, Parker RD, Sharma RP, Hughes BJ. 1990. Subclinical effects of groundwater contaminants. III. Effects of repeated oral exposure to combinations of benzene and toluene on immunologic responses in mice. *Arch Toxicol* 64:320-328.

Iavicoli I, Marinaccio A, Carelli G. 2005. Effects of occupational trichloroethylene exposure on cytokine levels in workers. *J Occup Environ Med* 47:453-457.

International Agency for Research on Cancer (IARC). 2014. Monographs on the Evaluation of Carcinogenic Risks to Humans. Trichloroethylene, tetrachloroethylene and some other chlorinated agents, vol 106, Lyon, France.

International Agency for Research on Cancer (IARC). 1995. Monographs on the Evaluation of Carcinogenic Risks to Humans Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals, vol 63, Lyon France.

International Agency for Research on Cancer (IARC). 1979. Monographs on the Evaluation of Carcinogenic Risks to Humans Some Halogenated Hydrocarbons, vol 20, Lyon France.

Ivanetich KM, Aronson I, Katz ID. 1977. The interaction of vinyl chloride with rat hepatic microsomal cytochrome P-450 in vitro. *Biochem Biophys Res Commun* 74(4):1411-1418.

Jedrychowski RA, Sokal JA, Chmielnicka J. 1985. Comparison of the impact of continuous and intermittent exposure to vinyl chloride, including phenobarbital effect. *J Hyg Epidemiol Microbiol Immunol* 29(2):111-120.

Jerina D, Daly J, Witkop B, et al. 1968. Role of arene oxide-oxepin system in the metabolism of aromatic substances I In vitro conversion of benzene oxide to a premercapturic acid and a dihydrodiol. *Arch Biochem Biophys* 128:176-183.

Jia Q, Zang D, Yi J, Dong H, et al. 2012. Cytokine expression in trichloroethylene-induced hypersensitivity dermatitis: An in vivo and in vitro study. *Toxicol Lett* 215:31-39.

John BA, Said N. 2017. Insights from animal models of bladder cancer: recent advances, challenges, and opportunities. *Oncotarget* 8:57766-57781.

Jorgovanovic D, Song M, Wang L, Zhang Y. 2020. Roles of INF- $\gamma$  in tumor progression and regression: a review. *Biomarkers Res* 8:49.

Joseph M, Enting D. 2019. Immune responses in bladder cancer-role of immune cell populations, prognostic factors and therapeutic implications. *Front Oncol* 9:1270.

Jubber I, Ong S, Bukavina L, Black PC, et al. 2023. Epidemiology of bladder cancer in 2023: a systematic review of risk factors. *Eur Urol* 84:176-190.

Kamijima M, Wang H, Yamanoshita O, Ito Y, Xia L, Yanagiba Y, Chen C, Okamura A, Huang Z, Qiu X, Song X, Cai T, Liu L, Ge Y, Deng Y, Naito H, Yoshikawa T, Tohyama M, Li L, Huang H, Nakajima T. 2013. Occupational trichloroethylene hypersensitivity syndrome: human herpesvirus 6 reactivation and rash phenotypes. *J Dermatol Sci*. 2013 Dec;72(3):218-24.



- Keil DE, Peden-Adams MM, Wallace S, Ruiz P, Gilkeson CS. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. *J Environ Sci Health Part A* 44:443-453.
- Khan MF, Wang G. 2018. Environmental agents, oxidative stress and autoimmunity. *Curr Opin Toxicol* 7:22-27.
- Kitamura T, Qian BZ, Pollard JW. 2015. Immune cell promotion of metastasis. *Nat Rev Immunol* 15: 73–86.
- Klaassen CD, ed. 2019. Casarett & Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill Education. ISBN10: 1259863743.
- Kondo T, Nakazawa H, Ito F, Hashimoto Y, et al. 2006. Favorable prognosis of renal cell carcinoma with increased expression of chemokines associated with a Th1-type immune response. *Cancer Sci* 97:780-786.
- Krajewski J, Dobecki M, Gromiec J. 1980. Retention of vinyl chloride in the human lung. *Br J Ind Med* 37(4):373-374. <https://doi.org/10.1136/oem.37.4.373>.
- Krause RJ, Lash LH, Elfarra AA. 2003. Human kidney flavin-containing monooxygenases and their potential roles in cysteine S-conjugate metabolism and nephrotoxicity. *J Pharmacol Exp Ther* 304(1):185-191.
- Koutros S, Deccker KL, Baris D, Pardo LA, et al. 2021. Bladder cancer risk associated with family history of cancer. *Int J Cancer* 148:2915-2923.
- Kunzli M, Masopust D. 2023. T cell memory. *Nature Immunol* 24:903-914.
- Kusuda T, Shigemasa K, Arihiro K, Fujii T, Nagai N, Ohama K. 2005. Relative expression levels of Th1 and Th2 cytokine mRNA are independent prognostic factors in patients with ovarian cancer. *Oncol Rep* 13:1153–1158.
- Lan Q, Zhang L, Li G, Vermeulen R, et al. 2004. Hematotoxicity in workers exposed to low levels of benzene. *Science* 306:1774-1776.
- Lan Q, Zhang L, Tang X, Shen M, et al. 2010. Occupational exposure to trichloroethylene is associated with a decline in lymphocyte subsets and soluble CD27 and CD30 markers. *Carcinogenesis* 31:1592-1596.
- Lash LH, Fisher JW, Lipscomb JC, Parker JC. 2000. Metabolism of trichloroethylene. *Environ Health Perspect* 108:177-200.
- Lash LH, Parker JC. 2001. Hepatic and renal toxicities associated with perchloroethylene. *Pharmacol Rev* 53(2):177-208.
- Lash LH, Chiu WA, Guyton K, Rusyn I. 2014. Trichloroethylene biotransformation and its role in mutagenicity, carcinogenicity and target organ toxicity. *Mut Res* 762:22-36.
- Lash LH. 2025. Trichloroethylene: an update on an environmental contaminant with multiple health effects. *Annu Rev Pharmacol Toxicol* 65:1-21.
- Lee KM, Bassig BA, Zhang L, Vermeulen RC, et al. 2019. Association between occupational exposure to trichloroethylene and serum levels of microRNAs: a cross-sectional molecular epidemiology study in China. *Int Arch Occup Environ Health* 92:1077-1085.

Lehmann I, Thoele A, Rehwagen M, et al. 2002. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environ Toxicol* 17:203-210.

Leibman KC, Ortiz E. Metabolism of halogenated ethylenes. 1977. *Environ Health Perspect*. 1977 Dec; 21:91-7. doi: 10.1289/ehp.772191. PMID: 612463; PMCID: PMC1475331.

Lenis AT, Lec PM, Chamie K. 2020. Bladder cancer a review. *JAMA* 324:1980-1991.

Levine B, Fierro MF, Goza SW, et al. 1981. A tetrachloroethylene fatality. *J Forensic Sci* 26:206-209.

Li S, Yu Y, Yang P, Wang, et al. 2018. Trichloroethylene alters Th1/Th2/Th17/Treg paradigm in mice: a novel mechanism for chemically induced autoimmunity. *Int J Toxicol* 37:155-163.

Li C, Li X, Zhang Z. 2024. Oxidative stress and pro-inflammatory cytokines following perchloroethylene exposure in young female dry-cleaning workers. *Work* 77:975-979.

Li W, Liu X, Yang X, Chen Y, et al. 2019. Effect of trichloroacetaldehyde on the activation of CD4+ T cells in occupational medicamentosa-like dermatitis: An in vivo and in vitro study. *Toxicol*. 423:95-104.

Liu SY, Qu HT, Sun RJ, Yuan D, Sui XH, Shan NN. 2022. High-throughput DNA methylation analysis in ITP confirms NOTCH1 hypermethylation through the Th1 and Th2 cell differentiation pathways. *Int Immunopharmacol* 111:109105.

Lokeshwar SD, Lopez M, Sarcan S, Aguilar K, et al. 2022. Molecular oncology of bladder cancer from inception to modern perspective. *Cancers* 14:2578.

Lovern MR, Maris ME, Schlosser PM. 1999. Use of a mathematical model of rodent in vitro benzene metabolism to predict human in vitro metabolism data. *Carcinogenesis* 20:1511-1520.

Lukaszewski T. 1979. Acute tetrachloroethylene fatality. *Clin Toxicol*. 1979;15(4):411-5. doi: 10.3109/15563657908989895. PMID: 540489.

Miller FW, Hess EV, Clauw DJ, Hertzman PA, et al. 2000. Approaches for identifying and defining environmentally associated rheumatic disorders. *Arthrit & Rheum* 43:243-249.

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

National Toxicology Program (NTP). 2015. U.S. Department of Health and Human Services, Report on Carcinogens. Monograph on Trichloroethylene, vol. 05, Research Triangle Park, North Carolina, USA.

Oldford SA, Robb JD, Codner D, Gadag V, et al. 2006. Tumor cell expression of HLA-DM associates with a Th1 profile and predicts improved survival in breast carcinoma patients. *Int Immunol* 18:1591-1602.

Ordaz JD, Damayanti NP, Irudayaraj MK. 2017. Toxicological effects of trichloroethylene exposure on immune disorders. *Immunopharmacol. Immunotoxicol.* 39:305-317.

Oronsky B, Caroen S, Reid T. 2022. What Exactly Is Inflammation (and What Is It Not?). *Int J Mol Sci* 23:14905.

Parham P. 2015. Editor, The Immune System, 4<sup>th</sup> Edition. Garland Science, Taylor & Francis Group (New York). Chapter 17 – Cancer and Its Interaction with the Immune System, 2015.

Park S, Rong L, Owczarek TB, Di Bernardo M, et al. 2021 Novel mouse models of bladder cancer identify a prognostic signature associated with risk of disease progression. *Cancer Res* 81:5161-5175.

Peden-Adams MM, Eudaly JG, Heesemann LM, Smythe J, Miller J, et al. 2006. Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice. *J Environ Sci Health A* 41:249-271.

Pegg DG, Zempel JA, Braun WH, et al. 1979. Disposition of (14C) tetrachloroethylene following oral and inhalation exposure in rats. *Toxicol Appl Pharmacol* 51:465-474.

Pérez VI, Van Remmen H, Bokov A, Epstein CJ, Vijg J, Richardson A. 2009. The overexpression of major antioxidant enzymes does not extend the lifespan of mice. *Aging Cell* 8:73-75.

Pessayre D, Wandscheer JC, Descatoire V, Dolder A, Benhamou JP. 1979. Effects of inducers on the in vivo covalent binding of a vinyl chloride metabolite to fractions. *Biochem Pharmacol.* 1979 Dec 15;28(24):3667-8. doi: 10.1016/0006-2952(79)90414-3. PMID: 533564.

Reddy VP. 2023. Oxidative Stress in Health and Disease. *Biomedicines* 11:2925.

Ristow M, Zarse K, Oberbach A, Klötting N, et al. 2009. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci U S A* 106:8665-8670.

Rosenthal GJ, Snyder CA. 1985. Modulation of the immune response to *Listeria monocytogenes* by benzene inhalation. *Toxicol Appl Pharmacol* 80:502-510.

Rosenthal GJ, Snyder CA. 1987. Inhaled benzene reduces aspects of cell-mediated tumor surveillance. *Toxicol Appl Pharmacol* 88:35-43.

Rozen MG, Snyder CA, Albert RE. 1984. Depressions in B- and T-lymphocyte mitogen induced blastogenesis in mice exposed to low concentrations of benzene. *Toxicol Lett* 20:343-349.

Rusyn I, Chiu WA, Lash LH, Kromhout H, et al. 2014. Trichloroethylene: mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. *Pharmacol Therapeut* 141:55-68.

Sabourin PJ, Chen BT, Lucier G, 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* 87:325-336.

Sanders VM, Tucker AN, White KL Jr, Kauffmann BM, Hallett P, Carchman RA, Borzelleca JF, Munson AE. 1982. Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water. *Toxicol Appl Pharmacol*. 1982 Mar 15;62(3):358-68. doi: 10.1016/0041-008x(82)90138-7. PMID: 7071855.

Savolainen H, Pfaffli P, Tengen M, et al. 1977. Biochemical and behavioral effects of inhalation exposure to tetrachloroethylene and dichloromethane. *J Neuropathol Exp Neurol* 36:941-949.

Schlichting LM, Wright PF, Stacey NH. 1992. Effects of tetrachloroethylene on hepatic and splenic lymphocytotoxic activities in rodents. *Toxicol Ind Health* 8:255-266.

Seiji K, Inoue O, Jin C, Liu YT, et al. 1990 Dose-excretion relationship in tetrachloroethylene-exposed workers and the effect of tetrachloroethylene co-exposure on trichloroethylene metabolism. 16:675-684.

Seo M, Yamagiwa T, Kobayashi R, Ikeda K, et al. 2008a. Augmentation of antigen-stimulated allergic responses by a small amount of trichloroethylene ingestion from drinking water. *Regul Toxicol Pharmacol* 52:140-146.

Seo M, Yamagiwa T, Kobayashi R, Ikeda K, et al. 2008b. A small amount of tetrachloroethylene ingestion from drinking water accelerates antigen-stimulated allergic responses. *Immunobiology* 213:663-669.

Seo M, Kobayashi R, Okamura T, Ikeda K, et al. 2012. Enhancing effects of trichloroethylene and tetrachloroethylene on type I allergic responses in mice. *J Toxicol Sci* 37:439-445.

Shariat SF, Milowsky MM, Droller MJ. 2009. Bladder cancer in the elderly. *Urol Oncol* 27:653-667.

Sharma RP, Gehring PJ. 1979 Immunologic effects of vinyl chloride in mice. *Ann. NY Acad Sci* 320:551-563.

Sharma RP, Yakel HO, Gehring PJ. 1980. Immunotoxicologic studies with vinyl chloride in rabbits and mice. *Int J Immunopharmacol* 2:295-299.

Singh N, Baby D, Rajguru JP, Patil PB, et al. 2019 Inflammation and cancer. *Ann Afr Med* 18:121-126.

Srbova J, Teisinger J, Skramovsky S. 1950. Absorption and elimination of inhaled benzene in man. *Arch Ind Hyg Occup Med* 2:1-8.

Tarkowski S, Wisniewska-Knypl JM, Klimczak J, Damiński W, Wróblewska K. 1980. Urinary excretion of thiodiglycolic acid and hepatic content of free thiols in rats at different levels of exposure to vinyl chloride. *J Hyg Epidemiol Microbiol Immunol*. 1980;24(3):253-61. PMID: 7003010.

Teng MW, Galon J, Fridman WH, Smyth MJ. 2015. From mice to humans: developments in cancer immunoediting. *J Clin Invest* 125:3338-3346.

Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, et al. 2011. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, Th2, Treg, Th17) in patients with colorectal cancer. *Cancer Res* 71:1263–1271.

Ubukata H, Motohashi G, Tabuchi T, Nagata H, et al. 2010. Evaluations of interferon- $\gamma$ /interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. *J Surg Oncol* 102:742–747.

USEPA. 2001. Health Assessment Document for Trichloroethylene Synthesis and Characterization (External Review Draft). US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, D.C., USA.

USEPA. 2011. Toxicological Review of Trichloroethylene. In support of summary information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, US Environmental Protection Agency, Washington, D.C., USA.

USEPA. 2020. Risk Evaluation for Trichloroethylene. 2020. National Center for Environmental Assessment, US Environmental Protection Agency, US Environmental Protection Agency, Washington, D.C., USA.

Vesalainen S, Lipponen P, Talja M, Syrjanen K. 1994. Histological grade, perineural infiltration, tumour-infiltrating lymphocytes and apoptosis as determinants of long-term prognosis in prostatic adenocarcinoma. *Eur J Cancer* 30A:1797–1803.

Volkel W, Friedewald M, Lederer E, et al. 1998. Biotransformation of perchloroethene: Dose-dependent excretion of trichloroacetic acid, dichloroacetic acid, and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. *Toxicol Appl Pharmacol* 153(1):20-27.

Wang G, Cai P, Ansari GA, Khan MF. 2007. Oxidative and nitrosative stress in trichloroethylene-mediated autoimmune response. *Toxicol* 229:186-193.

Wang L, He X, Bi Y, Ma Q. 2012. Stem cell and benzene-induced malignancy and hematotoxicity. *Chem Res Toxicol* 25:1303-1315.

Watanabe PG, McGowan GR, Madrid EO, et al. 1976b. Fate of [14C]vinyl chloride following inhalation exposure in rats. *Toxicol Appl Pharmacol* 37(1):49-59.

Wells MS, Nerland DE. 1991. Hematotoxicity and concentration-dependent conjugation of phenol in mice following inhalation exposure to benzene. *Toxicol Lett* 56:159-166. [https://doi.org/10.1016/0378-4274\(91\)90102-c](https://doi.org/10.1016/0378-4274(91)90102-c).

Wright PFA, Thomas WD and Stacey NH. 1991. Effects of trichloroethylene on hepatic and splenic lymphocytotoxic activities in rodents. *Toxicol* 70:231-242.

Xuequin Y, Wenxue L, Peimano L, Wen Z, et al. 2018. Cytokine expression and cytokine-based T cell profiling in occupational medicamentosa-like dermatitis due to trichloroethylene. *Toxicol Lett* 288:129-135.

Yang T, Luo W, Yu J, Zhang H, Hu M, Tian J. 2024. Bladder cancer immune-related markers: diagnosis, surveillance, and prognosis. *Front Immunol* 15:1481296.

Zhang J, Li N, Wang H, Shen T, Zhu Q. 2017. The immune response in trichloroethylene hypersensitivity syndrome. *Toxicol Ind Health* 33:876-883.

Zhang J, Yang Y, Huang H, Xie H, et al. 2022. TNF-/TNFR1 regulates the polarization of Kupffer cells to mediate trichloroethylene-induced liver injury. *Ecotoxicol Environ Safety* 230:11314.

Zhang L, Bassig BA, Mora JL, Vermeulen R, Ge Y. 2013. Alterations in serum immunoglobulin levels in workers occupationally exposed to trichloroethylene. *Carcinogenesis* 34:799-802.

Zhang N, Li D, Shao J, Wang X. 2015. Animal models for bladder cancer: The model establishment and evaluation. *Oncol Let* 9:1515-1519.

**APPENDIX A: CV OF MICHAEL J. McCABE, JR., PH.D**

**Michael J. McCabe, Jr., Ph.D.**  
**Toxicologist/Immunologist**

**PROFESSIONAL EXPERIENCE**

**2024 – Intertox, Inc., Seattle, Washington - Harleysville\*, Pennsylvania**

- **Principal Scientist, Toxicology and Immunology Expert**  
National expert performing technical investigations, analyses, research, written reports and testimony aimed at supporting opinions directed toward the resolution (e.g., settlement or verdict) of litigation or insurance matters involving alcohol, cannabinoids, drugs of abuse or misuse, medical devices, vaccines, and environmental or occupational exposures to chemical (i.e., toxicants) or biological (i.e., pathogens) agents and their effects on human health, behavior and performance.

**2017 – Temple University, Philadelphia, Pennsylvania**

- **Department of Chemistry; College of Science and Technology**  
Adjunct Associate Professor, Lecturer Forensic Toxicology; Master's level graduate students

**2019 – 2024 Exigent Group Limited, Cape Town, South Africa**

**2023 – 2024 Morae Global Corporation, Houston, Texas**

- **Executive Director Exigent Forensic Consulting**  
Had operational and technical oversight of a team of scientists and professionals who functioned as testifying experts in various disciplines including toxicology & pharmacology, liquor liability, human factors, clinical psychology, premises safety, biomechanics, etc.
- **Toxicology and Immunology Expert**  
Provided technical investigations, analysis, reports, and testimony involving the application of fundamental principles of toxicology and environmental medicine toward the resolution of torts and other litigation involving exposures to drugs, chemicals, xenobiotics and other environmental agents and stressors affecting human health and/or performance. Case examples involved the following:
 

<ul style="list-style-type: none"> <li>• alcohol</li> <li>• dram shop</li> <li>• cannabinoids/marijuana</li> <li>• opioids</li> <li>• other drugs of abuse/misuse (e.g., benzodiazepines, cocaine)</li> </ul>	<ul style="list-style-type: none"> <li>• carbon monoxide and other gases (e.g., hydrogen sulfide, chlorine, methane)</li> <li>• metals (e.g., lead, mercury, cobalt, zinc, nickel, arsenic, aluminum, etc.)</li> <li>• asbestos</li> <li>• pesticides and herbicides</li> <li>• solvents (e.g., BTEX, VOCs)</li> </ul>	<ul style="list-style-type: none"> <li>• medical devices</li> <li>• vaccines</li> <li>• carcinogens</li> <li>• food poisoning</li> <li>• skin/eye irritants</li> <li>• allergens</li> <li>• adverse drug reactions</li> </ul>
---	--	---

---

\* Dr. McCabe works from an office located in the greater Philadelphia area.



**2009 – 2019 Robson Forensic, Inc., Lancaster and Philadelphia, Pennsylvania**

- **Toxicology and Immunology Expert, 2009 - 2019**
- **Director of Practice Groups, 2014 - 2019**  
Accountable for technical oversight of expert work within all RFI Practice Groups (~100 experts). Responsibilities included recruiting, training, mentoring and quality assurance (peer review).
- **Science Practice Group Leader, 2012 - 2015; 2019**  
Responsible for case assignment, technical oversight and peer review of expert work within scientific disciplines including toxicology, pharmacology, immunology, pharmacy, liquor liability, arboriculture, animal (equine) science, environmental health and safety, industrial hygiene, water quality, blood spatter, food safety and questioned documents.

**2000 – 2017 University of Rochester Medical Center, Rochester, New York**

- **Department of Environmental Medicine; School of Medicine and Dentistry**  
**Adjunct Associate Professor** 2009 - 2017  
**Associate Professor** 2003 - 2009  
**Assistant Professor** 2000 - 2003
- **Research, Teaching and Administrative duties as follows:**  
**Research** - function as a Principal Investigator responsible for operational and fiscal management and oversight of an NIH-funded scientific research program centered on mechanistic metal toxicology and immunotoxicology. Supervised technical and intellectual efforts of approximately 25 scientists (Ph.D., M.S., B.S. levels) working on lab-based and epidemiological research projects.  
  
**Teaching** - instructional responsibilities within and across university-wide medical and graduate curricula including lecturing (topics included metal toxicity, cell signaling, immunity, ethics), course development (e.g., Course Director, Target Organ Toxicology), and laboratory supervision and mentoring of postdoctoral, graduate (Ph.D. and M.S.) and undergraduate trainees.  
  
**Administrative** - committee service in various capacities within the Environmental Health Sciences Center "*Environmental Agents as Modulators of Human Disease and Dysfunction*" (e.g., Director Immunomodulators and Immunopathogenesis Research Core), Toxicology Training Program (e.g., Deputy Director Toxicology Training Program, Curriculum Committee Chairman, Thesis Committee member on > 20 Ph.D. and M.S. dissertations), and appointments to various committees within the School of Medicine and the College (e.g., University Flow Cytometry Oversight Committee, Task Force to establish an Undergraduate Public Health Major).

**1992 – 2000 Wayne State University, Detroit, Michigan**

- Institute of Chemical Toxicology, Graduate School of Health Sciences**

**Assistant Professor 1997 - 2000**

**Adjunct Assistant Professor, Department of Pharmaceutical Sciences 1994 - 2000**

**Research Assistant Professor 1992 – 1997**

Established an extramurally-funded research program centered on mechanistic metal immunotoxicity. Responsible for teaching immunology and cellular biochemistry to graduate level students (Master's, Ph.D. and PharmD).

**Director, Imaging and Cytometry Facility Core, Environmental Health Sciences Center in Molecular and Cellular Toxicology with Human Applications 1997 - 2000**

Responsible for establishing and operating a state-of-the-art flow cytometry facility serving the needs of ~20 scientists engaged in molecular cell biology research projects requiring immunophenotyping, cell cycle analysis, apoptotic marker analysis, intracellular cytokine analysis, etc.

**1990 – 1992 Karolinska Institute, Stockholm, Sweden**

- Institute of Environmental Medicine, Postdoctoral Research Associate**

Training and research in mechanisms of toxicity, cell death, cell signaling, metal toxicology

**1985 – 1990 Albany Medical Center Hospital, Albany, New York**

- Pathology and Laboratory Medicine, Medical Technician, Serology and Blood Bank**

## **EDUCATION**

1991 Ph.D., Biomedical Studies (Microbiology and Immunology), Albany Medical College

1990 M.S., Biomedical Studies (Microbiology and Immunology), Albany Medical College

1984 B.S., Biology, Siena College, Loudonville, New York

1984 *In Vitro* Cell Biology and Biotechnology, State University of New York at Plattsburgh and the W.H. Miner Agricultural Research Center, Chazy, New York

## **Continuing Education and Certifications**

- An Introduction to Clinical and Medical Toxicology; Society of Toxicology Continuing Education Course; Nashville, TN, March 2023
- Certified as a Diplomate of the American Board of Toxicology; 2012 - 2021
- Fellow of the Academy of Toxicological Sciences (ATS); 2012 - 2018
- Ethics, Opioids and America's Drug Overdose Crisis; Society of Toxicology Webinar, December 2019
- TIPS Instructor Certification Training; TIPS/Health Communications, Inc., April 2018
- Ocular Toxicology. Pharmacology and Drug Delivery: An Eye to the Future. Society of Toxicology Contemporary Topics in Toxicology; San Francisco CA, June 2016

- New Horizons in Chemical Carcinogenesis: Advances in Mode of Action and Mechanism of Cancer Pathogenesis. Society of Toxicology Continuing Education Course; San Diego CA March 2015
- Toxicology and Regulatory Considerations for Combination Products. Society of Toxicology Continuing Education Course; San Diego CA, March 2015
- Advances in Safety Assessment of Medical Devices. Society of Toxicology Continuing Education Course; San Diego CA, March 2015
- 17th Annual Toxicology Teaching Day, Department of Emergency Medicine, Upstate Medical University/Upstate New York Poison Control Center; Syracuse NY, November 2013
- The Changing Faces of Antidotes. American College of Medical Toxicology; San Juan PR, March 2013
- Alcohol Abuse Academy: Current Perspectives on Impairment, Dependence and Withdrawal. American College of Medical Toxicology; San Juan PR, March 2013
- Basic Principles of Human Risk Assessment. Society of Toxicology Continuing Education Course; San Antonio TX, March 2013
- The REACH Regulation and Safety Assessment Approaches for Chemicals that Come in Contact with the Skin. Society of Toxicology Continuing Education Course; San Antonio TX, March 2013
- 16th Annual Toxicology Teaching Day, Department of Emergency Medicine, Upstate Medical University/Upstate New York Poison Control Center; Syracuse NY, November 2012
- Prescription Opioid Misuse Academy: The Dark Side of Prescription Opioids. American College of Medical Toxicology; San Diego CA, March 2012
- The Robert F. Borkenstein Course on The Effects of Drugs on Human Performance and Behavior. Indiana University: Center for Studies of Law in Action; Bloomington IN, April 2010
- The Robert F. Borkenstein Course on Alcohol and Highway Safety; Testing, Research and Litigation. Indiana University: Center for Studies of Law in Action; Bloomington IN, December 2009
- First Forensic Course: Ethanol and Marijuana. American College of Medical Toxicology; Baltimore MD, November 2009
- Servers and Managers Alcohol Responsibility Training (S.M.A.R.T.); Certified, 2009
- New Frontiers in Metal Toxicology; Genetic Susceptibility, Early Diagnosis, and Related Biological Indices. Society of Toxicology Continuing Education Course; Baltimore MD, March 2009
- Faculty Development Medical Education Leadership Series. University of Rochester School of Medicine and Dentistry; Rochester NY, 2007 - 2008
- Essentials of Metal Toxicology. Society of Toxicology Continuing Education Course; San Diego CA, March 2006
- Radiation and Radioisotope Safety Training. University of Rochester Medical Center Radiation Safety Unit; August 2000
- Certified Key Operator, Becton Dickinson Immunocytometry Systems FACSCalibur Cell Analyzer and Sorter, Training Course; Mansfield MA, December 1997

## PROFESSIONAL MEMBERSHIPS

- Society of Toxicology, 1989 - present
- American Chemical Society, 2012
- American Association of Immunologists, 2003 - 2008

## **HONORS AND AWARDS**

- Best Paper of the Year Award, Society of Toxicology, Immunotoxicology Specialty Section, 2009
- Outstanding Young Investigator Award, Society of Toxicology, Immunotoxicology Specialty Section, 2000
- Who's Who among Students at American Colleges & Universities, 1990
- Dean's Award for Excellence in Research, Albany Medical College, 1990
- Dean's Award for Excellence in Research, Albany Medical College, 1989
- Graduate Student Award for Excellence in Research, Society of Toxicology, Metals Specialty Section, 1989

## **EDITORIAL ASSIGNMENTS**

- Associate Editor, Toxicology and Applied Pharmacology, 2001 - 2013
- Editorial Board Member, Toxicology and Applied Pharmacology, 1999 - 2001
- Editorial Board Member, Toxicological Sciences, 2008 - 2015
- Editorial Board Member, Toxicology Letters, 2009 - 2013
- Editorial Board Member, Journal of Immunotoxicology, 2003 - 2013

Peer-reviewer for the following journals (selected list):

Environmental Health Perspectives  
 Toxicology  
 Journal of Immunology  
 Carcinogenesis  
 Critical Reviews in Toxicology  
 Chemical Research in Toxicology  
 Journal of Inorganic Biochemistry  
 Nutrition and Cancer  
 Cell Proliferation  
 Apoptosis  
 Cellular Microbiology  
 Journal of Pharmacy and Pharmacology  
 Journal of Biochemical and Molecular Toxicology  
 Journal of Applied Toxicology

## **INTERNATIONAL/NATIONAL ADVISORY HEALTH COUNCILS AND RESEARCH AND REGULATORY REVIEW COMMITTEES**



- ENVIRON International Corp., Environmental Exposures to Nickel and its Relationship to Disease: Respiratory Disease, Asthma and Cardiovascular Toxicity, Panelist, Arlington, VA, October 2012
- Department of Defense, U.S. Army Medical Research and Materiel Command, Congressionally Directed Medical Research Programs, Gulf War Illness Research Peer-Review Panel Chairman, October 2011
- National Institutes of Environmental Health Sciences, Division of Extramural Research and Training, Superfund Basic Research and Training Program Review Panel, 2011
- National Institute of Environmental Health Sciences, Expert Panel Workshop to Examine the Role of Environment in the Development of Autoimmune Disease, Expert Panelist and White Paper Co-Author, 2010
- U.S. Environmental Protection Agency - Workshop on Policy-Relevant Science to Inform and Plan for Review of the National Ambient Air Quality Standards for Lead, Expert Panelist, 2010
- World Health Organization/International Programme of Chemical Safety, Harmonization Project – Guidance Document for Risk Assessment of Mercury Immunotoxicity, 2009 - 2010
- Congressionally-Directed Medical Research Program (Department of Defense), Peer-Reviewed Medical Research Program Panel, (Gulf War Injury Proposals), 2000 - 2010, 2012, 2013
- National Research Council of the National Academies of Science, Committee on Beryllium Alloy Exposures, Managing Health Effects of Beryllium Exposure, The National Academy Press, 2007 - 2008
- National Institutes of Environmental Health Sciences, Division of Extramural Research and Training, Special Emphasis Review Panel, Interdisciplinary Partnerships in Environmental Health Sciences, 2006
- Center for Scientific Review, NIH Division of Research Grants, Skeletal Biology Structure and Regeneration Study Section, *Ad hoc* member, 2006
- Center for Scientific Review, NIH Division of Research Grants, Hypersensitivity, Autoimmune and Immune-mediated Disease Review Panel, *Ad hoc* member, 2006
- National Institute of Dental and Craniofacial Research, Special Emphasis Review Panel, Sjogren's Syndrome, 2006
- Environmental Protection Agency, External Reviewer, Air Quality Criterion for Lead, 2005
- Center for Scientific Review, NIH Division of Research Grants, Integrative and Clinical Endocrinology and Reproduction Study Section, *Ad hoc* Member, 2005
- Center for Scientific Review, NIH Division of Research Grants, ZRG1 MOSS Musculoskeletal R01 and Small Business Review Panel, 2005
- National Institutes of Environmental Health Sciences, Division of Extramural Research and Training, Special Emphasis Review Panel, Centers of Biomedical Research Excellence (COBRE), 2005
- National Workshop Research Asthma Disparities, 2005
- National Institutes of Environmental Health Sciences, Division of Extramural Research and Training, Superfund Basic Research and Training Program Review Panel, 2004-2005

- ALTX-4 (2) Special Emphasis Panel, Small Business Incentive Research Applications, 1999-2004
- Center for Scientific Review, NIH Division of Research Grants, Alcohol and Toxicology (ALTX-4) Study Section, *Ad hoc* Member, 1999 - 2003
- ALTX-4 (2) Special Emphasis Panel, Postdoctoral Fellowships, 2001
- ALTX-4 (2) Special Emphasis Panel, Minority Pre-doctoral Fellowships, 1999
- National Institutes of Environmental Health Sciences Special Review Panel, Biological Effects of Power Frequency Electromagnetic Fields (EMF), 1996

## PROFESSIONAL SERVICE ASSIGNMENTS

### National

- Society of Toxicology Ethics, Legal, Forensic and Societal Issues Specialty Section (2022 – present); Vice President (2022); President (2023/2024); Past-President (2024/2025)
- Society of Toxicology, Education Career Development Committee; Committee member, 2019 - 2021
- Society of Toxicology, Career Resources and Development Committee; Committee member, 2018 - 2019
- Society of Toxicology Metals Specialty Section; Councilor (2001 - 2004); Vice President-elect (2004); Vice President (2005); President (2006); Past-President (2007)
- Society of Toxicology Immunotoxicology Specialty Section; Program Committee (1999 - 2001), Executive Committee (1999 - 2000), Awards Committee (1999), Membership Committee Chairman (1997 - 2000); Councilor (2004 - 2006)

### University

- Deputy Director, Toxicology Training Program, University of Rochester, 2004 - 2008
- Chairman, Curriculum Committee, Toxicology Training Program, U. Rochester, 2006 - 2008
- Director, Immunomodulators and Immunopathogenesis Research Core, Environmental Health Sciences Center, University of Rochester, 2003 - 2008
- Member, Flow Cytometry Oversight Committee, University of Rochester, 2003 - 2009
- Fenn Award Committee (review/select best Ph.D. thesis), University of Rochester, 2006 - 2008
- Member, Admissions Committee, Toxicology Training Program, U. Rochester, 2001 - 2008
- Member, Policy Committee, Toxicology Training Program, U. Rochester, 2001 - 2008
- *Ad hoc* Member, Task Force on Public Health Undergraduate Major for the College, 2007
- Facilitator, Ethics and Professional Integrity Core Course, 2004 - 2008
- Member, Toxicology Training Program Retreat Committee, 2002 - 2007
- Coordinator, Environmental Health Sciences Center Seminar Series, 2000 – 2007

## INVITED PRESENTATIONS (Does not include CLE presentations)

- Over 25 invited seminars at universities and government agencies across the country including (2019) Wayne State University; (2018) Wright State University; (2009) St. John's University; U.S. Food and Drug Administration; (2008) Texas A&M University, New York University; (2005) West Virginia University; (2004) Karolinska Institute, University of Louisville, (2000) Boston University, University of Connecticut; (1999) New York University; (1998) Pennsylvania State University, University of Texas at Austin, Medical College of Virginia, Rutgers University
- Society of Toxicology Annual Meeting – Workshop Session, Complex Interpretations of Substance Detection and Impairment. *Sins of Our Fathers: Lessons Learned from the Evolution of Alcohol per se Limits to Driving Under the Influence of Drugs Policy*, Salt Lake City UT, March 2024.
- Society of Toxicology Annual Meeting – Ethics, Legal, Forensic and Society Issues Specialty Section, Inaugural Keynote Address, San Antonio TX, March 2018
- Society of Toxicology Annual Meeting – Informational Session, Lead: Children's Exposures and Current Regulatory Standards. *Current State of Lead Research and Children's Issues*, Baltimore MD, 2009
- Society of Toxicology Annual Meeting – Continuing Education Course, New Frontier in Metal Toxicology: Genetic Susceptibility, Early Diagnosis, and Related Biological Indices. *Cell Signal Pathways Targeted by Toxic Metals*, Baltimore MD, 2009
- Ohio Valley Society of Toxicology Annual Meeting – *Attenuation of Apoptosis by Heavy Metals: Signaling Pathways Involved and Potential Importance in Autoimmunity*, Lexington KY, 2004
- Society of Toxicology Annual Meeting – Symposium, Arsenic Disruption of Cell Cycle: Mechanisms and Effects on Apoptosis, Differentiation and Carcinogenesis. *Cell Cycle Dysregulation by Arsenite: Implications for Its Chemotherapeutic Actions*, Baltimore MD, 2004
- National Institute of Environmental Health Sciences, – Workshop, Environmental Factors in Autoimmune Disease. *Attenuation of Activation-Induced Cell Death: A Potential Mechanism Contributing to Mercury-Induced Autoimmunity*, Durham, NC, 2003
- Society of Toxicology Annual Meeting – Symposium, Molecular Mechanisms of Xenobiotic-Induced Autoimmunity, San Francisco CA, 2001
- Society of Toxicology Annual Meeting – Symposium, Metals and Disorders of Cell Accumulation: Modulation of Apoptosis and Cell Proliferation. *Mechanisms Contributing to Systemic Autoimmune Disease: Mercury-Induced Tyrosine Phosphorylation and Disruption of the CD95/Fas Apoptotic Death Pathway*, New Orleans LA, 1999



## EXTRAMURAL GRANT FUNDING

- NIH ROI ES029484, Understanding the connection between exposure to mercury, auto immunity and tolerance in B cells, Consultant, 09/09/2018 - 08/31/2024
- NIH R21 ES024476, Understanding the Role of Mercury Exposures in Disrupting Central Tolerance in B cells, Consultant, 08/01/2014 - 07/31/2016
- NIH R21 ES021285, Understanding the Influence of n-3-Polyunsaturated Fatty Acids on Pro-inflammatory Aspects of Mercury, Consultant, 08/01/2012 - 07/31/2014
- NIH R21 ES019228, Analysis of B Cell Receptor Signals Modified by Mercury, Consultant, 07/15/2010 - 06/30/2012
- NIH R01 ES012403, Death Receptor Signaling and Mercury Immunotoxicity, Principal Investigator, 04/01/2003 - 03/31/2008
- NIH R01 ES11000, Disruption of Lymphocyte Signal Transduction by Mercury, Co-Principal Investigator, 12/01/2001 - 11/30/2007
- NIH R21 ES10351, Mechanisms Contributing to Mercury-Induced Autoimmunity, Principal Investigator, 10/01/1999 - 09/30/2003
- NIH R25 RR123711, Environmental Cyberschoolhouse, Co-Principal Investigator, 09/01/1998 - 08/31/2002
- NIH P30 ES06639-S, Shared Instrument Grant-Analytical Flow Cytometer System, Co-Principal Investigator, 09/01/1997 - 08/31/1998
- NIH R29 ES07365, Mechanisms and Consequences of Immunomodulation by Lead, Principal Investigator, 08/01/1996 - 07/31/2002
- NIH R01 ES04040, Cellular and Molecular Toxicity of Lead, Co-Investigator, 08/01/1995 - 07/30/1999
- NIH R01 CA49935, Immunomodulation and Chemically Induced Carcinogenesis, Co-Principal Investigator, 12/01/1994 - 11/30/1997

## PEER-REVIEWED PUBLICATIONS

- Gill R., McCabe, Jr., M.J. and Rosenspire A.J. Low level exposure to inorganic mercury interferes with B cell receptor signaling in transitional type 1 B cells. *Toxicol. Appl. Pharmacol.* 330:22-29, 2017 PMID: 28668464.
- Gill R., Jen K.L., McCabe, Jr., M.J. and Rosenspire A.J. Dietary n-3 PUFAs augment caspase 8 activation in Staphylococcal aureus enterotoxin B stimulated T-cells. *Toxicol. Appl. Pharmacol.* 309:141-8, 2016 PMID: 27614254.
- Gill R., Lanni L., Jen K.L., McCabe, Jr., M.J. and Rosenspire A.J. Docosahexaenoic acid counteracts attenuation of CD95-induced cell death by inorganic mercury. *Toxicol. Appl. Pharmacol.* 282:61-7, 2015 PMID: 25461680.
- Gill R.F., McCabe Jr., M.J. and Rosenspire A.J. Elements of the B cell signalosome are differentially affected by mercury intoxication. *Autoimmun. Dis.* 2014:1-10, 2014 PMID: 239358.



- Songdej, N., Winters, P.C., McCabe, Jr., M.J., and van Wijngaarden E. A population-based assessment of blood lead levels in relation to inflammation. *Environ. Res.* 110:272-277, 2010. PMID: 20116055
- Stamatina E., Ziemba, S.E., Menard, S.L., McCabe, Jr., M.J. and Rosenspire, A.J. T Cell Receptor Signaling is Mediated by Transient Lck Activity Which is Inhibited by Inorganic Mercury. *FASEB J.* 23:1663-1671, 2009. PMID:19168706
- Yang, S., Yao, H., Rajendrasozhan, S., Chung, S., Edirisinghe, I., Valvo, S., Fromm, G., McCabe, Jr., M.J., Sime P.J., Phipps, R.P., Li, J., Bulger, M. and Rahman I. RelB is differentially regulated by I $\kappa$ B-Kinase(IKK) in B cells and mouse lung by cigarette smoke. *Am. J. Respir. Cell Mol. Biol.* 40: 147-158, 2009. PMID:18688039
- Williams, L.K., Oliver, J., Peterson, E.L., Bobbitt, K.R., McCabe, Jr., M.J., Smolarek, D., Havstad, S.L., Wegienka, G., Burchard, E.G., Ownby, D.R., and Johnson, C.C. Gene-environment interactions between CD14 C-260T and endotoxin exposure on Foxp3+ and Foxp3- CD4+ lymphocyte numbers and total serum IgE in early childhood. *Annals Allergy Asthma & Immunol.* 100:128-136, 2008. PMID: 18320914
- Farrer, D.G., Hueber, S. Laiosa, M.D., Eckles, K.G. and McCabe, Jr., M.J. Reduction of myeloid suppressor cell derived nitric oxide provides a mechanistic basis of lead enhancement of alloreactive CD4+ T cell proliferation. *Toxicol. Appl. Pharmacol.* 229:135-145, 2008. PMID: 18433816
- McNeely, S.C., Belshoff, A.C., Taylor, B.F., Fan, T.M., McCabe, Jr., M.J., Pinhas, A.J. and States, J.C. Sensitivity to sodium arsenite depends upon susceptibility to arsenite-induced mitotic arrest. *Toxicol. Appl. Pharmacol.* 229:252-261, 2008.
- Lehman, G. M. and McCabe, Jr., M.J. Arsenite Slows S Phase Progression Via Inhibition of cdc25A Dual Specificity Phosphatase Gene Transcription. *Toxicol. Sci.* 99:70-78, 2007.
- Laiosa, M.D., Eckles, K.G., Langdon, M., Rosenspire, A.J. and McCabe, Jr., M.J. Exposure to inorganic mercury *in vivo* attenuates extrinsic apoptotic signaling in Staphylococcal Enterotoxin B stimulated T-cells. *Toxicol. Appl. Pharmacol.* 225:238-250, 2007.
- McCabe, Jr., M.J., Laiosa, M.D., Li, L., Menard, S.L., Mattingly, R.R., and Rosenspire, A.J. Low and non-toxic inorganic mercury burdens attenuate BCR-mediated signal transduction. *Toxicol. Sci.* 99:512-521, 2007.
- Ziemba, S. E., Mattingly, R. R., McCabe, Jr., M. J., Rosenspire, A. J. Inorganic Mercury. Inhibits the activation of LAT in T cell receptor-mediated signal transduction. *Toxicol. Sci.* 89:145-153, 2006.
- McNeely, S.C., Xu X., Taylor B.F., McCabe, Jr., M.J., Zacharias W., States, J.C. Exit from arsenite induced mitotic arrest is p53-dependent. *Environ. Health Perspect.* 114:1401-1406, 2006.
- Taylor, B.F., McNeely, S.C., Miller, H.L., Lehmann, G. McCabe, Jr., M.J., States, J.C. P53 suppression of arsenite-induced mitotic catastrophe is mediated by p21. *J. Pharmacol. Exper. Therapeut.* 318:142-151, 2006.
- McCabe, Jr., M. J., Whitekus, M. J., Hyun, J., Langdon, M., Clarkson, T. W., and Rosenspire, A. J. Attenuation of CD95-Induced Apoptosis by Inorganic Mercury: Caspase-3 Is Not a Direct Target of Hg<sup>2+</sup>. *Toxicol. Lett.* 155:161-170, 2005.

- Ziemba, S. E., McCabe, Jr., M. J., Rosenspire, A. J. Inorganic Mercury Dissociates Pre-assembled Fas/CD95 Receptor Oligomers in non-apoptotic T lymphocytes. *Toxicol. Appl. Pharmacol.* 206:334-342, 2005.
- McCollum, G., Keng, P., States, J. C., and McCabe, Jr. M. J. Arsenite Delays Myeloid Leukemia Cells in Each Cell Cycle Phase and Induces Apoptosis Following G2/M Arrest. *J. Pharmacol. Exp. Therapeut.* 313:877-887, 2005.
- Farrer, D. F., Hueber, S., and McCabe, Jr., M. J. Lead Enhances CD4+ T Cell Proliferation Indirectly by Targeting Antigen Presenting Cells and Modulating Antigen-Specific Interactions. *Toxicol. Appl. Pharmacol.* 207:125-137, 2005.
- Joseph, C.L.M., Havstad, S., Ownby, D.R., Peterson, E.L., Maliarik, M., McCabe, Jr., M. J., Barone, C., and Cole-Johnson, C. Blood Lead Level and risk of Asthma. *Environ. Health Perspect.* 113:900-904, 2005.
- McCabe, Jr., M. J., Whitekus, M. J., Hyun, J., Eckles, K. G., McCollum, G., and Rosenspire, A. J. Inorganic Mercury Attenuates CD95-mediated Apoptosis by Interfering with Formation of the Death Inducing Signaling Complex. *Toxicol. Appl. Pharmacol.* 190:146-156, 2003.
- McCabe, Jr., M. J. Mechanisms and Consequences of Silica-Induced Apoptosis. *Toxicol. Sci.* 76:1-2, 2003.
- McCabe, Jr., M. J., Singh, K. P., and Reiners, Jr., J. J. Low-level Lead Exposure In Vitro Stimulates the Proliferation and Expansion of Alloantigen-reactive CD4high T Cells. *Toxicol. Appl. Pharmacol.* 177:219-231, 2001.
- Lawrence, D. A. and McCabe, Jr., M. J. Immunomodulation by Metals. *Int. Immunopharmacol.* 234:293-302, 2002.
- Guity, P., McCabe, Jr., M. J., Santini, R. P., Pitts, D., and Pounds, J. P. Protein Kinase C Does not Mediate the Actions of Lead on the Vitamin-D3-Dependent Production of Osteocalcin. *Toxicol. Appl. Pharmacol.* 178:109-116, 2002.
- States, J. C., Reiners, Jr., J. J., Pounds, J. G., Kaplan, D. J., Beauerle, B. D., McNeeley, S. C., Mathieu, P., and McCabe, Jr., M. J. Arsenite Disrupts Mitosis and Induces Apoptosis in SV40-Transformed Human Skin Fibroblasts. *Toxicol. Appl. Pharmacol.* 180:83-91, 2002.
- Mattingly, R. R., Felczak, A., Chen, C., McCabe, Jr., M. J., and Rosenspire, A. J. Low Concentrations of Inorganic Mercury Inhibit Ras Activation During T Cell Receptor-mediated Signal Transduction. *Toxicol. Appl. Pharmacol.* 176:162-168, 2001.
- Waalkes, M. P., Fox, D. A., States, J. C., Patierno, S. R., and McCabe, Jr., M. J. Forum: Metals and Disorders of Cell Accumulation: Modulation of Apoptosis and Cell Proliferation. *Toxicol. Sci.* 56:255-261, 2000.
- Ben-Ozer, E. Y., Rosenspire, A. J., McCabe, Jr., M. J., Worth, R. G., Kindelskii, A. L., Warra, N. S., and Petty, H. R. Mercuric Chloride Damages Cellular DNA by a Non-Apoptotic Mechanism. *Mut. Res.* 470:19-27, 2000.
- McCabe, Jr., M. J. Singh, K. P., Reddy, S. A., Chelladurai, B. S., Pounds, J. G., Reiners, Jr., J. J., and States, J. C. Sensitivity of Myelomonocytic Leukemia Cells to Arsenite-Induced Cell Cycle Disruption, Apoptosis and Enhanced Differentiation is Dependent on the Interrelationship Between Arsenic Concentration, Duration of Treatment and Cell Cycle Phase. *J. Pharmacol. Exp. Therapeut.* 295: 724-733, 2000.

- Whitekus, M. J., Santini, R. P., Rosenspire, A. J., and McCabe, Jr., M. J. Protection Against CD95-mediated Apoptosis by Inorganic Mercury in Jurkat T Cells. *J. Immunol.* 162:7162-7170, 1999.
- McCabe, Jr., M. J., Santini, R. P., and Rosenspire, A. J. Low and Non-Toxic Levels of Ionic Mercury Interfere with the Regulation of Cell Growth in the WEHI-231 B Cell Lymphoma. *Scand. J. Immunol.* 50:233-241, 1999.
- Pokorski, P. L., McCabe, Jr., M. J., and Pounds, J. G. Lead inhibits meso-2,3-Dimercaptosuccinic Acid Induced Calcium Transients in Cultured Rhesus Monkey Kidney Cells. *Toxicol.* 134:19-26, 1999.
- Pokorski, P. L., McCabe, Jr., M. J., and Pounds, J. G. DMSA Induces Calcium Transients in Cultured Rhesus Monkey Kidney Cells. *Toxicol.* 138:81-91, 1999.
- McCabe, Jr. M. J., Singh, K. P., and Reiners, Jr., J. J. Delayed Type Hypersensitivity is Impaired in Lead Intoxicated Mice. *Toxicol.* 139:255-264, 1999.
- Rosenspire, A. J., Bodepudi, S., Mathews, M., and McCabe, Jr., M. J. Low Levels of Ionic Mercury Modulate Protein Tyrosine Phosphorylation in Lymphocytes. *Int. J. Immunopharm.* 20:697-707, 1998.
- Jiang, S. A., Chow, S. C., McCabe, Jr., M. J., and Orrenius, S. Lack of Ca<sup>2+</sup> Involvement in Thymocyte Apoptosis Induced by Chelation of Intracellular Zn<sup>2+</sup>. *Lab. Invest.* 73(1):111-117, 1995.
- McCabe, Jr., M. J. and Orrenius, S. Genestein Induces Apoptosis in Immature Human Thymocytes by Inhibiting Topoisomerase-II. *Biochem. Biophys. Res. Comm.* 194(2):944-950, 1993.
- McCabe, Jr., M. J., Jiang, S. A., and Orrenius, S. Chelation of Intracellular Zn<sup>2+</sup> Induces Apoptosis in Mature Thymocytes. *Lab. Invest.* 69(1):101-110, 1993.
- Chow, S. C., Kass G. E. N., McCabe, Jr., M. J., and Orrenius, S. Tributyltin Increases Cytosolic Free Ca<sup>2+</sup> Concentration in Thymocytes by Mobilizing Intracellular Ca<sup>2+</sup>, Activating a Ca<sup>2+</sup> Entry Pathway, and Inhibiting Ca<sup>2+</sup> Efflux. *Arch. Biochem. Biophys.* 298(1):143-149, 1992.
- McCabe, Jr., M. J. and Lawrence, D. A. Lead, a Major Environmental Pollutant, Is Immunomodulatory by Its Differential Effects on CD4<sup>+</sup> T Cell Subsets. *Toxicol. Appl. Pharmacol.* 111:13-23, 1991.
- McCabe, Jr., M. J., Dias J. A., and Lawrence, D. A. Lead Influences Translational or Post-translational Regulation of Ia Expression and Increases Invariant Chain Expression in Mouse B Cells. *J. Biochem. Toxicol.* 6(4):269-276, 1991.
- McCabe, Jr., M. J. and Lawrence, D. A. The Heavy Metal Lead Exhibits B Cell Stimulatory Factor Activity by Enhancing B Cell Ia Expression and Differentiation. *J. Immunol.* 145(2):671-677, 1990.

## BOOK CHAPTERS

- Lynes, M.A., Pietrosimone, K., Marusov, G., Donaldson, D.V. Tarracciano, C., Yin, X., Lawrence, D.A. and McCabe, Jr., M.J. Metal Influences on Immune Function. In, Cellular and Molecular Biology of Metals, J. Koropatnick and R. Zalups (eds), Taylor & Francis, pp. 379 – 414, 2010.



- Dietert, R.R. & McCabe, Jr., M. J. Lead Immunotoxicity, In, Immunotoxicology and Immunopharmacology, 3rd edition, R. Luebke, R. House, and I. Kimber (eds), Raven Press, pp. 207-224, 2005.
- McCabe, Jr., M. J. Lead. In, Metal Immunotoxicology, J. Zelikoff and P. T. Thomas (eds), Taylor & Francis, pp. 111-130, 1998.
- McCabe, Jr., M. J. T Cell Regulatory Functions. In, Comprehensive Toxicology, volume V, D. A. Lawrence (volume editor), I. G. Sipes, C. A. McQueen, A. J. Gandolfi (eds), Elsevier Pergamon Press, pp. 261-278, 1997.
- McCabe, Jr., M. J. and Pounds, J. G. The Calcium Messenger System. In, Comprehensive Toxicology, volume I, J. J. Bond (volume editor), I. G. Sipes, C. A. McQueen, A. J. Gandolfi (eds), Elsevier Pergamon Press, pp. 255-274, 1997.
- Lawrence, D. A. and McCabe, Jr., M. J. Immune Modulation by Toxic Metals. In, Metal Toxicology, R. A. Goyer, M. P. Waalkes, and C. D. Klaassen (eds), Academic Press, pp. 305-337, 1995.
- McCabe, Jr., M. J. and Orrenius, S. Protein Kinase C: A Key Enzyme Determining Cell Fate in Apoptosis? In, "Protein Kinase C", J. F. Kuo (ed), Oxford University Press, pp. 290-304, 1994.
- McCabe, Jr., M. J. Mechanisms and Consequences of Immunomodulation by Lead. In, Immunotoxicology and Immunopharmacology, 2nd edition, J. H. Dean, M. I. Luster, A. E. Munson, and I. Kimber (eds), Raven Press, pp. 143-162, 1994.
- McCabe, Jr., M. J. and Lawrence, D. A. The Effects of Metals on the Development of the Immune System. In, Xenobiotics and Inflammation, L. B. Schook and D. L. Laskin (eds), Academic Press, pp. 193-216, 1994.
- Kowolenko, M., McCabe, Jr., M. J., and Lawrence, D. A.. Metal-induced Alterations of Immunity. In, Clinical Immunotoxicology, D. S. Newcombe, N. R. Rose, J. C. Bloom (eds), Raven Press, pp. 401-420, 1992.
- McCabe, Jr., M. J. and Lawrence, D. A. Aspects of Lead Potentiation of B Lymphocyte Responses and Their Relationship to Immune Dysregulation. In, Metal Ions in Biology and Medicine, P. Collery, L. A. Poirer, M. Manfait, and J. C. Etienne (eds), John Libbey Eurotext, Paris, pp. 271-276, 1990.
- Lawrence, D. A., McCabe, Jr., M. J., and Kowolenko, M. Metal Influences on the Incidence of Autoimmunity and Infectious Disease. Ibid, pp. 237-242, 1990.

#### **LETTERS, EDITORIALS, SHORT ARTICLES AND OTHER CONTRIBUTIONS**

- Waalkes, M. P., Fox, D. A., States, J. C., Patierno, S. R., and McCabe, Jr., M. J. Forum: Metals and Disorders of Cell Accumulation: Modulation of Apoptosis and Cell Proliferation. Toxicol. Sci. 56: 255-261, 2000.
- McCabe, Jr., M. J. and Orrenius, S. Deletion and Depletion: Involvement of Viruses and Environmental Factors in T-lymphocyte Apoptosis. Lab.Invest. 66:403-406, 1992.
- McCabe, Jr., M. J., Nicotera, P., and Orrenius, S. Calcium-dependent Cell Death: Role of the Endonuclease, Protein Kinase C, and Chromatin Structure. Ann. N. Y. Acad. Sci. 663:269-278, 1992.

- Orrenius, S., McCabe, Jr., M. J., and Nicotera, P.  $\text{Ca}^{2+}$  -dependent Mechanisms of Cytotoxicity and Programmed Cell Death. *Toxicol. Let.* 64/65:357-364. 1992.

## TEACHING

### Lecturing:

- Adjunct Associate Professor, Temple University, Philadelphia, PA; Department of Chemistry, Course Director – Forensic Toxicology, 2017, 2018, 2019, 2020, 2021, 2022, 2023
- Forensic Immunotoxicology; New York University School of Medicine, 3 hours/year, 2020
- Principles of Toxicology, New York University School of Medicine, Lecturer – Overview of Forensic Toxicology; 1.5 lecture hours/year, 2011 - 2013; 2017, 2018
- Society of Toxicology Undergraduate Diversity Program. Fundamentals of Forensic Toxicology, Society of Toxicology Annual Meeting, Baltimore, MD, Presenter, March 12, 2017
- CJFI410, Advanced Crime Scene Forensics, Colorado Technical University, undergraduate, "Overview of Forensic Toxicology," 2015
- TOX-501, Forensic Pathology, University of Rochester School of Medicine, Toxicology Training Program, Course Co-Director, 2012, 2014
- Environmental Immunotoxicology, New York University School of Medicine, Lecturer – Signal Transduction Mechanisms; 3 lecture hours/year, 2010, 2012
- Forensic Science, University of New Haven, Lecturer – Alcohol & Drug Toxicology, March 2011
- TOX-590, Reproductive Toxicology, University of Rochester School of Medicine, Toxicology Training Program, Lecture – Reproductive Immunotoxicology; 2 lecture hours/year, 2007
- TOX-522, Target Organ Toxicology, University of Rochester, Toxicology Training Program, Lecturer – Metal Toxicology; 2 lecture hours/year, 2007
- TOX-521, Molecular Toxicology, University of Rochester School of Medicine, Toxicology Training Program, Lecturer – Apoptosis; 2 lecture hours/year, 2006 - 2008
- TOX-595, Current Topics in Immunotoxicology, University of Rochester, Toxicology Training Program, Course Director, 1.5 hours/week/semester, 2005 - 2009
- IND-501, Ethics and Professional Integrity in Research, University of Rochester School of Medicine, Graduate Education Curriculum, Group Facilitator; 6 lecture hours/year, 2005 - 2008
- TOX-521 & 522, Molecular Toxicology, University of Rochester School of Medicine, Toxicology Training Program, Course Director, 2005 - 2007
- TOX-595, Seminars in Toxicology, University of Rochester School of Medicine, Toxicology Training Program, Course Director, 2005 – 2007
- TOX-522, Target Organ Toxicology, University of Rochester School of Medicine, Toxicology Training Program, Lecturer; Innate Immunity; 2 lecture hours/year, 2008 – 2010; Autoimmune Diseases; 2 lecture hours/year, 2007 – 2009; Metal Toxicology; 2 lecture hours/year, 2007; Immunotoxicology; 8 lecture hours/year, 2004 - 2008

- Year Two Case Seminars, HD- Emerging Diseases and The Environment, University of Rochester School of Medicine, Medical Student Curriculum, Lecturer – Lead Poisoning, 2004 - 2007
- Workshop Leader, University of Rochester School of Medicine, Toxicology Training Program, How to Write a Research Paper, 2004 - 2007

Thesis Adviser – Graduate Students and Post-doctoral Fellows Trained

- Michael A. Laiosa, Ph.D. (2006 - 2008) University of Rochester, Toxicology Training Program, Postdoctoral Fellow
- David Farrer, Ph.D. (2002 - 2006) University of Rochester, Toxicology Training Program, Thesis: Target Cells and Key Mediators in Lead-Induced Immune Modulation
- Geniece McCollum, Ph.D. (2001 - 2006) University of Rochester, Toxicology Training Program; Thesis: Mechanism of Arsenic-Induced Growth Inhibition of a Myeloid Leukemia Cell Line
- Michael J. Whitekus, Ph.D. (1996 - 2000), Wayne State University, Multidisciplinary Program in Molecular and Cellular Toxicology. Thesis: Inorganic Mercury and Dysregulation of Fas-Mediated Apoptosis
- Parto Guity, Ph.D. (1993 - 1998), Wayne State University, Department of Pharmaceutical Sciences. Thesis: Effect of Lead on Vitamin-D-Induced Osteocalcin Secretion: Involvement of Protein Kinase C
- Philip Pokorski, Ph.D. (1993 - 1997), Wayne State University, Department of Pharmaceutical Sciences. Thesis: Effects of Lead on Renal Proximal Tubule Cells and the Restorative Effects of Dimercaptosuccinic Acid in Treatment of Lead Poisoning

Member of more than 25 Ph.D. and M.S. thesis dissertation committees and qualifying examinations over the past 30 years.

**APPENDIX B: LIST OF PRIOR TESTIMONY FOR MICHAEL J. MCCABE, JR.,  
PH.D.**

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony – Rule 26**

4/8/2021	State of Utah vs. William Travis Fryer Seventh District Juvenile Court, Grand County, Utah Case No. 1183385 Trial Defendant
6/24/2021	KRISTA GENO, as Personal Representative of the Estate of JOSEPH KENT TWYMAN, Deceased v. TYLER WYATT GILLILAND, WAL-MART STORES, EAST, L.P. and SHIKI 2, LLC, d/b/a Shiki Japanese Restaurant Case No: CJ-2014-6041 District Court of Oklahoma City Trial Plaintiff
8/18/2021	Stephen Blighton, as personal representative of the Estate of Victoria Christine Blighton, Plaintiff v. Family Fun and Sports of Marianna, LLC, d/b/a Beef 'O' Brady's 14 <sup>th</sup> Judicial Circuit in and for Jackson County, Florida Case No.: 2019 CA 514 Deposition Defendant
8/19/2021	Darren Findling, Personal Representative for the Estate of Junior Clifford Martin, Deceased, Plaintiff v. Douglas Augustyniak and Nutrien AG Solutions, Inc. Defendants, et al. Circuit Court for the County of Van Buren, Michigan Case No.: 2020-070145-NI Deposition Plaintiff
9/15/2021	Constance Christopher, Plaintiff v. Wal-Mart Stores East I, LP et al. Circuit Court of Buchanan County, Missouri Case No. 20BU-CV-00950 Deposition Plaintiff
10/21/2021	Stephen Blighton, as personal representative of the Estate of Victoria Christine Blighton, Plaintiff v. Family Fun and Sports of Marianna, LLC, d/b/a Beef 'O' Brady's 14 <sup>th</sup> Judicial Circuit in and for Jackson County, Florida Case No.: 2019 CA 514 Deposition Defendant



**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

12/9/2021	Stephen Blighton, as personal representative of the Estate of Victoria Christine Blighton, Plaintiff v. Family Fun and Sports of Marianna, LLC, d/b/a Beef 'O' Brady's 14 <sup>th</sup> Judicial Circuit in and for Jackson County, Florida Case No.: 2019 CA 514 Trial Defendant
1/12/2022	Taronica L. McCormick, Administrator of the Estate of Dwayne K. McCormick, Plaintiff, v. Robert D. Huang, M.D.; Jose Sarao, M.D.; Ear Nose and Throat Group of New Jersey; Union Surgery Center Superior Court of New Jersey, Middlesex County Docket No. MID-L-2720-20 Deposition Plaintiff
4/26/2022	Harvey Mahler, Plaintiff, vs. Vitamin Shoppe Industries, Inc., d/b/a The Vitamin Shoppe, Defendants Case No. 19-CV-03848 United States District Court for the Northern District of Illinois Eastern Division Deposition Defendant
5/9/2022	Travis S. Sweigart, Plaintiff, vs. Voyager Trucking Corp. and Kevin J. Patten, Defendants Case No. 5:21-CV-00922-EGS United States District Court for the Eastern District of Pennsylvania Deposition Defendant
5/10/2022	Gae Guagenti, Administrator of the Estate of John Guagenti, Deceased, Plaintiff, vs. Bobcat of Lima, Inc., et al., Defendants Case No. CV 2021 0018 State of Ohio, County of Allen, In the Court of Common Pleas Deposition Defendant
5/12/2022	Juan Gonzalez, et al. Plaintiffs vs. Uno Chicago Grill, et al. Defendants Docket No. Mid-K-7308-16 Superior Court of New Jersey Law Division: Middlesex County Deposition Defendant

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

5/16/2022	Todd and Lindsay Powers, Plaintiffs, vs. City of Geneva, Defendant Index No. 116046-2017 State of New York Supreme Court, County of Ontario Trial Defendant
6/3/2022	Louis A. Boni, III and Kasie Boni, Plaintiffs, vs. Tios Lak, LLC, Defendants Case No. 2020-CP-07-01436 State of South Carolina, County of Beaufort Court of Common Pleas, 14 <sup>th</sup> Judicial Circuit Deposition Defendant
6/6/2022	Mandy Sturmer and Cole Sturmer (A minor), Martha Brice & Gary Brice vs. Felicia Wallace, The Whistle Stop Inn, Inc & Westfield Insurance Company, Defendants Cause No: 49D03-1802-CT-008019 State of Indiana, County of Marion Marion Superior Court Deposition Defendant
6/8/2022	Deborah Monnahan, et al., Plaintiffs v. Modine Manufacturing Company, et al., Defendants
9/23/2022	Case No. 18CM-CC00218 Circuit Court of Camden County, Missouri Deposition Plaintiff
6/10/2022	Louis A. Boni, III and Kasie Boni, Plaintiffs, vs. Tios Lak, LLC, Defendants Case No. 2020-CP-07-01436 State of South Carolina, County of Beaufort Court of Common Pleas, 14 <sup>th</sup> Judicial Circuit Trial Defendant
7/15/2022	Karolina Twarowski, et al., Plaintiffs, vs. Heart's Desire, DCL, LLC, et al., Defendants Civil Action: 1:20-cv-00815-SAG United States District Court for the District of Maryland Northern District – Civil Division Deposition Plaintiff

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

8/16/2022	Ellis Morganfield Plaintiff, And Shamron Henry-Murray Plaintiff, vs. Francis Marion Barnett, IV, Elevated Restaurant Group, LP And KCI USA, Inc. Defendants Cause No. 2019CI05163 Consolidated With Cause No. 2019CI08623 District Court of Bexar County, Texas; 285 <sup>th</sup> Judicial District Deposition Defendant
9/21/2022	Lynn Sharp, Plaintiff vs. Heitzenrater's Hideout, LLC d/b/a The Hideout and John Heitzenrater, Defendants No. GD-16-000945 Court of Common Pleas of the Fifty-Ninth Judicial District; Elk County, Pennsylvania Trial Defendant
9/27/2022	Wendy Landree, Plaintiff, vs. Christopher Schweikert, The Park Tap & Grill, Heilongjiang Barn, LLC, et al. Defendants Docket No.: MID-L-7897-18 Superior Court of New Jersey Law Division: Middlesex County Trial Defendant
11/9/2022	Denise Bradshaw, As Administratrix of the Estate of David Bradshaw III and Amanda Gordon, as Guardian for David Bradshaw IV and Denise Bradshaw, Plaintiffs vs. India Thompson, Individually and in her Official Capacity and Lexington-Fayette Urban County Government, Defendants Civil Action No. 19-CI-03277 Commonwealth of Kentucky; Fayette Circuit Court Deposition Plaintiff
11/15/2022	Michael Broderick and Ilene Broderick, Plaintiffs, against Edgewater Park Owners Cooperative, Inc., Edgewater Park Athletic Assoc., Inc., Edgewater Park Volunteer Hose Co. No. 1, Inc. and Edgewater Park Athletic Association Corp., Defendants Supreme Court of the State of New York, County of Bronx Trial Plaintiff
11/17/2022	Isaac Flowers, as Successor Personal Representative of the Estate of Cedar Flowers, Deceased, Plaintiff, v. Medicine Wheel, Inc., D/B/A Milburn Family Medicine Clinic, Paul Weathers, Heather Workman, RJRX, LLC, D/B/A Sooner Pharmacy of Tishomingo, Parks Family Dental, PC and Justin Parks, Defendants Case No. CJ-2019-00020 District Court of Johnston County, State of Oklahoma Deposition Plaintiff

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

11/29/2022	William Traylor, Plaintiff; v. Apache Corporation and Pioneer Energy Services Corp., Defendants Cause No. 2018-21167 District Court of Harris County, Texas; 164 <sup>th</sup> Judicial District Deposition Defendant
1/20/2023	Alison S. Inga v. Nature's Bounty Company Case Number: 9:2020cv81513 US District Court for the Southern District of Florida Deposition Plaintiff
4/24/2023	Michael T. Powell, John M. Yarbough, Sheila D. Yarbough and Gabriel C. Fells vs. Tequillas, Inc., Tequilas, Inc. d/b/a Tequila's Mexican Restaurant Bar & Grill, Richard Ceja, New Punjab Ltd. Co., New Punjab Ltd. Co, d.b.a Fuel Point, Nakaash Ali, Shahrukh Ali, Fahad Momin and Luis Fernando Torres Cause No. E-206286 District Court of Jefferson County, Texas Hearing Plaintiff
6/14/2023	Ronnie Trigg, et al. v. Justin Eberle, Field Box St. Peters LLC, and Hattrick's Irish Sports Pub, LLC Case No. 21SL-CC00813 Circuit Court of the Twenty-First Judicial Circuit. St. Louis County, Missouri Deposition Defendant
6/15/2023	Stephen F. Pekach and Kimberly N. Pekach, H/W Plaintiffs, v. Kelly's Seafood, Inc. d/b/a Kelly's Seafood d/b/a Kelly's Seafood Restaurant d/b/a Kelly's Seafood Restaurant and Bar and Brett William Kelly, Defendants No. 01812 Court of Common Pleas, Philadelphia County Trial Defendant
7/13/2023	Estate of Michael A. Hanfeld, c/o Tracey M. Hanfeld, Special Administrator, Tracy M. Hanfeld, Plaintiff, Medical Associates/Mercy Family Care Network, LLC, Involuntary Plaintiff, vs. Commercial Recreation Specialists, Inc., Hawkeye Boat Sales, Inc. North Sports, Inc. (d/b/ Aqualgide), Connelly Skis HoldCo, Inc. Guangzhou Asia Inflatables, Co. Limited, et al. Defendants Case No. 21-CV-272 State of Wisconsin, Circuit Court Grant County Deposition Plaintiff

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

7/19/2023	Kellie and Forrest Benner, Plaintiffs, vs. Tacky Jacks; Estate of Shannon Clark; Matt Harris; et al. Case Number: CV-2020-901029 Circuit Court of Baldwin County, Alabama Deposition Plaintiff
8/3/2023	William Byrne, as Administrator of the Estate of Margaret Leja, deceased, Plaintiff, vs. Mark Burak, as Special Administrator of the Estate of Paul C. Burak, deceased, the Catholic Bishop, a corporation sole, d/b/a Archdiocese of Chicago, and Square Celt, LLC, an Illinois Limited Liability Company, d/b/a Square Celt Ale House & Grill, Defendants No. 19 L 4088 Circuit Court of Cook County, Illinois Deposition Plaintiff
8/8/2023	Willie Smith, Plaintiff, vs., Rite Aid, Walgreen Co., Walgreen Boots Alliance, et al., Defendants Docket No. ESX-L-3355-20 Superior Court of New Jersey: Essex County Deposition Defendant
8/22/23	Deborah Monnahan, et al., Plaintiffs v. Modine Manufacturing Company, et al., Defendants Case No. 18CM-CC00218 Circuit Court of Camden County, Missouri Trial Plaintiff
9/7/2023	Amritpaul Singh Athwal, and Harprit Kaur Athwal, Plaintiffs, v Volvo Trucks North America, Inc., Volvo Group North America, LLC, and Webasto Thermo & Comfort North America, Inc., Defendants Case No. 1:22-cv-00044-HAB-SLC United States District Court for the Northern District of Indiana; Fort Wayne Division Deposition Plaintiff
9/25/2023	Kristen Pym Plaintiff, v. Ford Motor Company and Robert Armstrong Defendants Cause No: 19SL-CC00857 Circuit Court of Missouri; Twenty First Judicial Circuit (St. Louis County) Deposition Plaintiff

**Michael J. McCabe, Jr., Ph.D.**

**History of Expert Testimony**

10/26/2023	Ruth Halpine, Plaintiff, vs. Gulf Shores Tacky Jack's LLC; et al., Defendants Civil Action No. CV-22-901088 Circuit Court of Baldwin County, Alabama Deposition Plaintiff
3/29/2024	Joanne M. Moitoza and John R. Souza, Individually and as Co-Administrators of the Estate of John J. Souza, Plaintiffs, vs. Sarah E. Bergbenholtz, a/k/a Sarah Becker, Ivan, Inc. d/b/a Federal Taphouse and Kitchen, et al. Civil Action No. PC 2019-6835 Superior Court, Providence, Rhode Island Deposition Defendant
4/9/2024	Donald Beckerdite, Plaintiff, v. Bar Three LLC D/B/A Brewbakers, MCBCO Brewery, LLC D/B/A Martin City Brewing Company, and Delbert Hannah, by and through Kevin Jones, Defendant <i>ad litem</i> Case No. 22CA-CC00299 The Circuit Court of Cass County, Missouri Deposition Plaintiff
5/29/2024	Lukas T. Udris, Plaintiff, vs. Brandon H. Christianson, and Kansas City Bier Company, LLC, Defendants Case No.: 2216-CV10212, Div. 12 Circuit Court of Jackson County, Missouri at Independence Deposition Plaintiff
8/27/2024	Caroline Patton Griffin, Individually and as Surviving Spouse and Executor of the Estate of Lee Dixon Griffin, Jr., Plaintiff, v. Toyota Motor Corporation, Toyota North America, Inc.; Toyota Motor Sales, U.S.A., Inc.; Toyota Motor Engineering & Manufacturing North America, Inc.; Toyota Manufacturing, Texas, Inc.; and Jim Ellis Automotive Holdings, Inc., Defendants Civil Action File No.: 1:23-cv-03107-TWT, United States District Court for the Northern District of Georgia Atlanta Division Deposition Plaintiff
12/16/2024	Daron L. Glenn Plaintiff v. Ford Motor Company; McMahon Associates, Inc.; Ramos & Associates, Inc.; Armour & Sons Electric; Obafemi Taiwo; Autoliv; PennDOT; City of Philadelphia; Tyreese Wheeler, Defendants No. 01479 Court of Common Pleas County of Philadelphia Trial Defendant