Exhibit 108

General Causation Expert Report of
KATHLEEN M. GILBERT, PHD

TCE, Non-Hodgkin Lymphoma, and Leukemia

Prepared by:

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Contents

I. INTRODUCTION

I was asked to provide my opinions concerning the role of trichloroethylene (TCE) in the development of NHL and leukemia in individuals who lived in and/or worked at Camp Lejeune Marine Base in North Carolina between 1953 and 1987. A summary of my qualifications as relevant to this report is described below, while my complete CV (which includes my publications during the last 10 years, and my trial and deposition testimony experience) can be found in Appendix A. My previous trial and deposition testimony experience has been limited to one previous trial testimony, one hearing, and five depositions in unrelated cases. If called as a witness, I could and would competently testify to the matters set forth in this report. All of my opinions are expressed to a reasonable degree of scientific certainty, and I reserve the right to amend these opinions should new information be made available to me. I may also provide supplemental opinions regarding this case, if requested.

The contaminants of interest at Camp Lejeune site include TCE, perchloroethylene (PCE), vinyl chloride, and benzene. These toxicants were present in the water from approximately 1953 to 1987. My report will focus on TCE since that is the contaminant that has been the nexus of my own research. However, the other contaminants will be discussed as sources of added toxicity.

II. BACKGROUND AND QUALIFICATIONS

My qualifications as an expert witness stem from more than 35 years of experience as a scientist/toxicologist conducting bench research in immunology, immunotoxicology, and human health toxicology. I have been funded by the National Institutes of Health (NIH) and the Environmental Protection Agency (EPA) to study the health impacts of adult- and developmental-exposure to TCE. I also received a $1.5 million grant from the Arkansas Biosciences Institute for developing an Immunotoxicology Center in Arkansas. Based on my expertise, I have been asked to review grants for the National Science Foundation, the EPA, and several study sections of the National Institute of Environmental Sciences (NIH), including the Superfund Basic Research (ZES1 LWJ-M), and Career Award Applications for the National Institute of Environmental Sciences.

I retired from the University of Arkansas for Medical Science (UAMS) as a tenured NIH-funded Full Professor in 2017. My work at UAMS was preceded by positions at The Scripps Research Institute in La Jolla, CA; the National Institute for Medical Research in London, UK; and Memorial Sloan-Kettering Cancer Center in New York, NY.

I have published 13 book chapters, and over 80 peer-reviewed publications, more than 30 of which are directly concerned with the health effects of TCE and/or its metabolites. Those publications examined:

- How TCE exposure at different life stages (fetal, early life, or adult) impacts its toxicity.[1-6]
- How TCE exposure impacts the immune system at the disease, tissue, cellular, genetic, and epigenetic level.[1, 7-17]
- How coexposure to other chemicals or lifestyle risk factors impact TCE-induced toxicity[6, 18]
- How TCE causes neurotoxicity[3, 4]

- How TCE exposure alters the gut microflora in ways that may promote systemic toxicity[19]
- How mathematical modeling can be used to examine TCE-induced immunotoxicity.[20]

My research on TCE-induced health effects is well regarded in the scientific community. For example, I was asked by the publishers of Springer/Humana Press to edit the 2014 book entitled *Trichloroethylene: Toxicity and Health Risks*, (Springer/Humana Press New York/Heidelberg). Springer/Humana Press has published a series of excellent books on how environmental toxicants impact human health. They are used to provide reliable information for the professional practice of environmental and natural scientists, as well as human and veterinary medicine.

In recognition of my expertise in TCE toxicity and human health, I have been asked several times over the years by different federal agencies—including the National Research Council, the National Academy of Sciences, and the NIH's National Toxicological Program – to review various TCE-related health risk documents. These included: *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*, 2006; *USEPA TSCA Workplan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses,* 2013*;* a possible change in listing status for TCE in the *Report on Carcinogens*, 2014; and *DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene,* 2019.

Lastly, I was nominated for and subsequently accepted a position as one of the founding members of the Scientific Advisory Committee on Chemicals (SACC) for the EPA from 2017 to 2021. The SACC is tasked with providing independent advice and expert consultation on issues related to the implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amends the Toxic Substances Control Act (TSCA). We reviewed EPA risk evaluations for 10 chemicals between 2017 and 2021 including: **TCE**, **perchloroethylene** (**PCE)**, carbon tetrachloride, methylene chloride, 1-bromopropane, n-methyl pyrrolidone, 1,4-dioxane, pigment violet 29, and cyclic aliphatic bromide cluster. I was tasked with providing opinions on the EPA's assessment of the human health effects of these chemicals.

A more comprehensive summary of my qualifications is set forth in my CV.

To prepare this report, I have invoiced my time at the rate of $400/hour. For deposition and trial testimony, my hourly rate is $500/hour.

III. MATERIALS USED TO FORM OPINIONS

During my many years working with TCE, I have read hundreds of studies concerning the health outcomes of TCE exposure, as well as studies that examined the relevant modes of action. My opinions about TCE toxicity are based in part on that cumulative literature review. Since it would be impossible for me to list all the manuscripts that I have read over the many years I have studied and performed work related to TCE, the references cited in this report should be considered representative rather than exhaustive, and I reserve the right to call upon my exhaustive research and experience with TCE literature should I be called to testify in this case.

In addition to peer-reviewed published manuscripts, I also relied on the following federal reports:

US EPA's Toxicological Review of Trichloroethylene of 2011.
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

Addendum to the Toxicological Profile for Trichloroethylene published by the Agency for Toxic Substances and Disease Registry in 2013.
https://www.atsdr.cdc.gov/toxprofiles/tce_addendum.pdf

Morbidity study of former Marines, employees, and dependents potentially exposed to contaminated drinking water at US Marine Base Camp Lejeune; Agency for Toxic Substances and Disease Registry, April 2018.
https://www.atsdr.cdc.gov/sites/lejeune/docs/health_survey_report-508.pdf

The importance of animals in the science of toxicology: Society of Toxicology Animals in Research Public Policy Statement, 1999
https://www.toxicology.org/pubs/docs/air/AIR_Final.pdf

US EPA's Final Risk Evaluation for Trichloroethylene (CASRN: 79-01-6) November 2020
https://www.epa.gov/sites/production/files/2020-11/documents/1._risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf

US EPA's Final Risk Evaluation for Perchloroethylene (Ethene,1,1,2,2-Tetrachloro) (CASRN: 127-18-4) December, 2020. Final Risk Evaluation for Perchloroethylene CASRN:127-18-4 (epa.gov)

ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases
https://www.atsdr.cdc.gov/sites/lejeune/docs/atsdr_summary_of_the_evidence_for_causality_tce_pce_508.pdf ("ATSDR Assessment of Evidence")

US EPA's 2023 Trichloroethylene: Regulation Under the Toxic Substances Control Act
https://www.govinfo.gov/content/pkg/FR-2023-10-31/pdf/2023-23010.pdf

Contaminated water supplies at Camp Lejeune. Assessing potential health effects
https://nap.nationalacademies.org/download/12618

Risk Evaluation for Perchloroethylene (Ethene,1,1,2,2-Tetrachloro-)
file:///C:/Users/gilbe/Downloads/EPA-HQ-OPPT-2019-0502-0058_CONTENT.PDF

Toxicological Profile for Vinyl Chloride https://www.atsdr.cdc.gov/ToxProfiles/tp20.pdf

IV. PROCESSES USED TO FORM OPINIONS

The opinions described in this report are based upon my education, training, and experience as a scientist/toxicologist and are all made to a reasonable degree of scientific certainty. My opinions in this report were arrived at using the same methodology I employ in other projects such as conducting TCE research, preparing peer-reviewed manuscripts, writing research grants, assessing federal regulatory documents, and making causal determinations between toxicants and diseases in other contexts.

In brief, my opinions are based on:

- Thirty-five years of experience as an immunologist, and 25 years of experience as an immunotoxicologist and human health toxicologist. This includes a well-developed understanding of correct scientific principles and methodologies.

- My own extensive peer-reviewed and NIH-funded research on TCE and disease outcomes.

- Experience on the SACC that included my invited professional review of the *EPA 2020 Risk Evaluation for Trichloroethylene*[2] and the *EPA 2020 Risk Evaluation for Perchloroethylene*.[26]

As identified above, my causation opinions for TCE are in part informed by the evaluation conducted by the EPA in its 2020 *Risk Evaluation for Trichloroethylene* and the ATSDR in its A*ssessment of Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases*.[21, 23] As discussed in greater detail throughout my report, I independently assessed the sources relied upon by these agencies in reaching my opinions in this case and performed my own independent analysis.

To form their causation opinions, both agencies (EPA and ATSDR) used a weight-of-evidence (WOE) approach. The WOE is defined as "*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.*"[1] The EPA WOE approach integrates data from epidemiological, animal, and mechanistic studies. I also employ a weight-of-evidence approach in reaching my opinions in this case, which is the standard practice of experts, including myself, in my fields of expertise.

To meet the high scientific standards for the literature reviews included in their reports, EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* (https://19january2021snapshot.epa.gov/sites/static/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf). This process complements the Risk Evaluation process in that it collects data. The data evaluation and data integration stages of the systematic review process are used to develop exposure and hazard assessments based on reasonably available information.

It is important to note that the conclusions reached by the EPA do not represent the opinion of a single individual or a single agency. As required by the TSCA, the EPA 2020 *Final Risk Evaluation for Trichloroethylene* [21] was reviewed by the members of the SACC. This committee contains wide-ranging expertise, including but not limited to risk assessors, epidemiologists, statisticians, toxicologists, and industry representatives. I was one of the SACC members that participated in the review of TCE. The evaluation was held in a public meeting in which anyone could register to make comments. Cumulatively, dozens of scientists and non-scientists weighed in on the evaluation, and general a

[1] Available at https://beta.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

consensus was reached regarding TCE causation. For these reasons, it is my opinion that the conclusions reached by the EPA, and which I describe here, are carefully reasoned and scientifically valid.

The evaluations conducted by the EPA and ATSDR were based on the modified Bradford Hill considerations. In 1965, Professor Hill gave a talk in which he described nine "viewpoints" to consider while determining disease causation.[24] This list included temporality of exposure, strength of exposure, dose-response determination, plausibility, elimination of alternative explanations, consistency/reproducibility, experiment (e.g. alleviation of toxicity by preventing or removing exposure), coherence, and specificity. These common-sense considerations are not a strict checklist, and this fact was recognized by Professor Hill himself, when he says, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*." Although Bradford Hill as a framework for critical thinking continues to be very useful, the field of toxicology has evolved to include new technologies and new fields of study (e.g. molecular toxicology). A modified Bradford Hill approach reflects these changes and is more comprehensive in its inclusion of all applicable data (animal studies, *in vitro* studies, and epidemiological studies).

Similar to the EPA and the ATSDR I used a modified Bradford Hill approach to derive my opinions. This means I considered results from epidemiological, animal, and mechanistic (sometime *in vitro*) studies. The importance of these three components in determining a causal relationship will be described below.

With respect to the causation standard I employed in reaching my opinions, I have reviewed the Camp Lejeune Justice Act (CLJA) and am aware the causation standard under the CLJA explains that Plaintiffs in this case must show "the relationship between exposure to the water at Camp Lejeune and the harm is—(A) sufficient to conclude that a causal relationship exists; or (B) sufficient to conclude that a causal relationship is at least as likely as not." *ATSDR Assessment of Evidence*, referenced above, considers the "at least as likely as not" standard to be the functional equivalent of its category for "equipoise and above." Although my opinions in this case are expressed to the higher "more likely than not" standard, the ATSDR's definition of "equipoise and above" served as guidance for me in this case. These classifications and categories are consistent with my education, training and experience and with the sciences to which they relate.

A. Importance of Epidemiological Studies

Epidemiological studies examine the direct real-life relationship between exposure to a particular toxicant and its associated toxicity. They are very useful in providing proof of concept that exposure to a particular toxicant is associated with a specific pathology. This approach is obviously relevant for human risk evaluation and circumvents the need to extrapolate animal or *in vitro* exposure levels to human equivalence.

If epidemiological studies do exist and provide relevant information, they are often considered as the highest potential level of evidence in determining causal relationships. However, epidemiology studies are sometimes limited in terms of documenting precise toxicant exposure, and in terms of providing different tissues and cell types for confirmatory mechanistic information. They also often examine occupational exposure rather than environmental exposure because the former is far easier to document. If someone encounters a toxicant outside of the workplace, they are often unaware of it. And in many cases, including Camp Lejeune, people are often unaware of their environmental exposures

until many years later, if ever. Thus, human studies are augmented by animal and *in vitro* models, which can circumvent some of the limitations of epidemiological studies.

B. Importance of Animal Studies

As stated in the Society of Toxicology Animals in Research Public Policy Statement:

> "In the absence of human data, research with experimental animals is the most reliable means of detecting important toxic properties of chemical substances and for estimating risks to human and environmental health."[2]
>
> *"If there is sufficient human data to describe the exposure-response relationship for an adverse outcome(s) that is judged to be the most sensitive effect(s), reference values should be based on human data. If sufficient human data are not available, data from animal studies must be employed with appropriate interspecies and intraspecies extrapolation factors."*[3]

Animal models have many advantages when examining chemical toxicity:

- Toxicant exposure is carefully administered and monitored. This makes it easier to evaluate dose-dependent and time-dependent effects. Such studies would obviously be unethical in humans.

- Animal models can be used to evaluate the effects of toxicant exposure on specific life stages (i.e., infants and the elderly).

- Animal models have advantages over the use of cultured cells, even if human in origin, to study toxicity. For example, any disease with immune system involvement, including myriad conditions including hematopoietic cancers, involves multiple cellular interactions. It is currently impossible to mimic the complex interactions that cause immunotoxicity in humans using individual populations of cultured cells. Instead, a sophisticated physiological system, such as can only be found in an intact animal, is needed to recapitulate complex diseases such as cancer.

Mice and humans share over 90% of the same genes, and are strikingly similar in terms of anatomy, physiology, and drug metabolism. It is undeniable that information obtained in mouse models is very often relevant to humans. For example, immune-based cancer vaccines and new cancer therapeutics known as immune checkpoint inhibitors, which are widely used to treat many types of cancer, were initially developed in mouse models before being successfully translated into human clinical trials.

It is also relevant to note that the vast number of chemicals identified in the environment or introduced as commercial products have never been tested for carcinogenicity. Unlike clinical trials that test

[2] Available at https://beta.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.
[3] *See* https://beta.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

chemicals with intended therapeutic value, testing these other chemicals for their carcinogenicity in humans has long been considered unethical.

Thus, animal models, especially mouse models, recapitulate human systems very well, and are often used to estimate the effects of toxicants on human health.

C. Importance of Mechanistic Studies

In addition to information obtained from epidemiological studies and animal models, it is standard in the scientific community, as well as in agencies such as the EPA, to incorporate mode of action (MOA) evidence into WOE causation determinations. Defining MOA (sometimes called mechanism of action or adverse outcome pathway) means identifying key events between exposure and pathology. Mechanistic research elucidates the cellular, biochemical, and molecular basis of chemical toxicity. The EPA's 2014 *Framework for Human Health Risk Assessment to Inform Decision Making* discussed the importance of identifying MOA in the risk assessment process.[4]

Understanding the MOA can inform causal relationship by:

(i) Supporting a designation of causation;

(ii) Confirming relevance of data from animals or *in vitro* studies for human health risk assessments;

(iii) Harmonizing causal relationship for various health endpoints;

(iv) Defining conditions under which a chemical is likely to cause an adverse effect;

(v) Helping to generate pharmacologic and nonpharmacologic strategies to counteract the adverse outcomes of chemical exposure.

Lastly, mechanistic information uncovered while studying a specific toxicant can help unravel the complex mechanisms of disease onset and progression and define the role of environmental insult in idiopathic disease.

Defining MOA often uses complimentary toxicokinetic and toxicodynamic evaluations.

Toxicokinetics includes information about the absorption, distribution, metabolism, and excretion of a toxicant. Toxicokinetic data for many chemicals are determined by using PBPK (physiologically based pharmacokinetic) modeling. This is a widely used and widely accepted mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion of toxicants in humans and other animal species. PBPK models can be used to convert animal exposures into human equivalent exposures.

Toxicodynamics defines the processes by which a toxicant, once it has been absorbed, distributed, and metabolized, interacts with the body to cause adverse effects. Toxicodynamic data is derived from

[4] Available at https://beta.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

human, animal, and *in vitro* studies. MOA data from human subjects is most often derived from blood samples since examination of other tissues is often logistically and ethically problematic. Animal models, however, expand the types and numbers of samples (blood and multiple tissues) that can be collected and examined. The EPA also uses mechanistic data derived from *in vitro* experiments (some of which use human cell types as targets) when synthesizing evidence for causation.

V. SUMMARY OF NHL AND LEUKEMIA ETIOLOGY

Lymphoid cancers arise in the immune system from genotoxic events that occur within immature lymphoid cells in the bone marrow or immature peripheral blood (leukemias), or more mature cells in the peripheral organs (non-Hodgkin's lymphoma). Similar to other types of cancer, NHL, and leukemia arise from genetic aberrations that induce a selective growth advantage of the malignant clone.

The discussion of how TCE promotes NHL and leukemia will be prefaced by a brief description of these two cancer types.

A. NHL epidemiology

Non-Hodgkin's Lymphoma (NHL) consists of a group of over 60 specific types of blood cancers that includes all lymphomas except Hodgkin's lymphomas. They are derived from mature lymphocytes, both T cells and B cells. New cases of NHL account for approximately 4.3% of all cancer cases in the US. The most recently reported incidence was 18.6/100,000 in 2017. The most recent reported incidence was 18.6/100,000 in 2017.[25] The most common NHL subtypes in developed countries are diffuse large B-cell lymphoma (DLBCL) (about 30%) and follicular lymphoma (about 20%).

B. Leukemia epidemiology

Unlike NHL, which involves transformation of mature lymphocytes, leukemia is initiated in the bone marrow and involves transformation of hematopoietic stem cells that were destined to be B cells, T cells, NK cells, or eosinophils.[26] Its main subtypes include acute lymphoblastic, acute myelogenous, chronic lymphocytic, and chronic myelogenous. The age-adjusted incidence rate of leukemia in the US is approximately 12.8/100,000. The age-adjusted incidence rate of leukemia in the US is approximately 12.8/100,000.

A detailed account of the different NHL and leukemia subtypes is beyond the scope of this report. The analysis will focus on characteristics shared by at least most of the subtypes.

C. NHL and leukemia share risk factors that highlight the role of the immune system in their etiology

Both NHL and leukemia are associated with immune dysfunction that encompasses both generalized inflammation and tumor-specific suppression. The inflammation associated with NHL etiology encompasses several pathways, including increased production of pro-inflammatory cytokines such as IL-6 and TNF-α.[27, 28] In addition to chronic inflammation, the opposite side of the immune spectrum, namely immune suppression, also plays a crucial role in the development of NHL and leukemia. In fact, adaptive immune response deficiency is the best characterized and strongest known risk factor for hematopoietic cancers.[29]

Many intrinsic and extrinsic risk factors identified for hematopoietic cancers such as increased age, smoking, obesity, and infection, are also associated with immune suppression and/or chronic inflammation. [30] [31]

There is ample evidence that exposure to toxicants such as TCE can promote the development of NHL and leukemia. The epidemiological evidence of this is presented in Tables I and II. Moreover, as discussed in Opinion 2, TCE promotes the kind of immune dysfunction, both chronic inflammation and immunosuppression, associated with NHL and leukemia.

VI. OPINION 1. TCE MORE LIKELY THAN NOT CAUSES NHL AND LEUKEMIA

This causation determination is based on epidemiological, animal, mechanistic studies, and the conclusions of federal agencies such as the EPA and ATSDR.

A. Epidemiological studies

I began my epidemiological review of TCE by reviewing those studies identified in the 2017 ATSDR Assessment of the Evidence. I also reviewed the EPA 2020 Risk Evaluation of Trichloroethylene, which included epidemiological studies published between 2017 and 2020. Both the ATSDR and the EPA have defined a systemic review methodology used to determine whether a study (i) meets the basic criteria that make it eligible for consideration, and (ii) provides reliable and useful information.[32] https://www.epa.gov/sites/ default/files/2015-07/documents/lit-studies.pdf [23]I found the ATSDR's and EPA's methodology for reviewing the epidemiology to be thorough and scientifically-valid based on my years of experience and training as a scientist. Lastly, I used PubMed (the free online NIH-sponsored database of medical science studies) to identify epidemiological studies published between 2020 and 2024. Any new federal reports or regulatory documents published since 2020 were also included in my literature search.

For inclusion in the epidemiological assessment of NHL and leukemia that I performed, studies had to demonstrate (1) a temporal relationship between chemical exposure and negative health effects (i.e. exposure precedes toxicity) and (2) convincing positive associations represented by a Risk Ratio (RR), Odds Ratio (OR), Standardized Mortality Ratio (SMR), or Standardized Incident Ratio (SIR) greater than 1.1, (3) biological plausibility, (4) adult exposure, (5) exposure durations of more than one month, and (6) ability to distinguish TCE-specific effects.

Once those basic requirements were met, I evaluated epidemiological studies to determine which studies have the highest utility. In line with the ATSDR standards, the studies were evaluated for:

1. **Confounding bias.** All the studies presented here were evaluated for whether possible confounding variables – such as exposure to smoking or other risk factors – were taken into account. This could mean that actual data from the participants were used to eliminate possible bias. Alternatively, other approaches (e.g., noting that smoking in a subset of the participants was similar in both controls and exposed) may have been used to conclude that confounding was unlikely.

2. **Exposure assessment**. Most occupational exposure studies used some kind of Job Exposure Matrix (JEM) to estimate TCE exposure. Some studies used actual on-site measurements or bio-monitoring to estimate exposure.

3. **Likely exposure.** Exposure miscalculation can be lessened if the results were observed in the population determined to be the most likely to be exposed to the highest concentrations of TCE or exposed for the longest duration. Thus, values associated with the highest or most likely exposure to TCE were shown here.

4. **Exposure-duration relationships.** Since an exposure-dependent or duration-dependent relationship between chemical exposure and pathology can add extra weight for causation, the studies described here were evaluated for this criterion.

5. **Incidence vs mortality**. The ATSDR gives weight to those studies that examined incidence rather than mortality.

6. **Meta-analysis**. As noted by the ATSDR, a meta-analysis is given extra weight since it represents the statistical analysis of multiple studies. Its pooled approach to data evaluation can lessen the biases and errors of individual studies.

Included in the epidemiological studies tables were the four studies conducted for the ATSDR by Bove *et al*. which examined cases of NHL and leukemia in both civilians and Marines who were exposed to the contaminated water at Camp Lejeune. In addition to the ORs for the highest or most likely TCE exposure, any reported data concerning the lowest duration or exposure level to cause disease (threshold info) were included in the tables.

Table I. Epidemiological studies showing that TCE and other chemicals cause NHL										
Studies	**Type**	**OR, RR, SIR,SMR**	**95% CI**	**Exposure**	**Threshold info**		**Confounder adjustment**	**Exposure-duration**	**Incidence vs Death**	**Meta-analysis**
					Exposure or Duration OR	**95% CI**				
Anttila[33]	Occup. Cohort	VOC 2.13 TCE 3.24 PCE 3.2	 1.06-3.80 0.67-9.45 0.39-11.6	Measured	 < 100 µmol/L TCA 2.01	 0.65-4.7			✓	
Bahr [34]	Occup. Cohort	TCE 1.76	1.09-2.69	JEM			Smoking, age, gender			
Blair[35]	Occup. Cohort	2.0 M/F 3.8 F	0.9-4.6 0.8-18.9	JEM	Low level intermittent exposure 1.5 M 3.9 F < 5 Unit years 1.8 M 3.8 F	 0.5-4.3 0.8-18 0.6-5.4 0.8-19				
Bove [36] Marines	Environ. Retro Cohort	VOC 2.17 TCE 1.97 VC 1.99 Benzene 1.94	0.63-7.5 0.55-7.03 0.56-7.13 0.54-6.95	Historical Measures			smoking, race and rank	✓		
Bove [37] Incidence	Environ. Retro Cohort	VOC Civilians1.31	0.84-2.03	Historical Measures	1-21 quarters at Camp Lejeune		Smoking, alcohol, age		✓	
Cocco[38]	Occup. Case-Con	2.2	0.7-6.7	JEM	≤ 5 ppm 1.1	0.4-3.0	Age, gender		✓	✓
Cohn [39]	Environ. Cohort			Measured	TCE		Age, gender		✓	

					Low grade NHL 0.1 - 5 ppb 1.29 F 1.36 M Int grade NHL > 5 ppb 1.66 F 1.59 M Hi grade NHL > 5 ppb 2.43 F 0.1-5 ppb 1.54 M <u>PCE</u> Hi grade NHL > 5 ppb 2.66 F	1.0-1.7 1-1.81 1.1-2.6 1.0-2.4 1.0-6.1 0.7-3.2 1.3-5.6				
Hansen [40]	Occup. Cohort	3.5 M	1.5-6.9	Measured	<u>< 19 mg/m^3</u> 3.9	1.1-10	Age		✓	
Hansen [41]	Occup. Cohort	1.26	0.89-1.73	Measured	5-25 Mg/L <u>TCA in urine</u> 1.16	0.53-3.09	Age		✓	✓
Karami [42]	Occup. Case-Con + Cohort	**<u>Cohort</u>**: Incidence 1.66 Mortality 1.41 **<u>Case-Con</u>** 1.42 Studies that confirmed TCE exposure <u>with urine</u> 2.15	1.29-2.14 1.11-1.78 0.86-2.33 1.34-3.45	JEM Measured	Cohort: Less <u>than 2-6.25 yrs</u> 1.3 Case-control <u>Low duration</u> 1.3	0.92-1.84 0.92-1.84			✓	✓
Mandel[43]	Occup. Cohort + Case-Con	<u>Cohort</u> 1.59	1.21-2.08	JEM Measured					✓	✓
Purdue [44]	Occup. Case-Con	1.4	0.8-2.4	JEM	1-60 ppm-hr Average weekly <u>exposure</u> 1.6 <u>1-6 Yrs. exposed</u>	0.7-3.8 1.0-4.7	age, gender		✓	

					2.1					
Raaschou-Nielsen [45]	Occup. Cohort	1.2 M 1.4 F	0.98-1.52 0.73-2.34	JEM	1 - 4.9 yrs duration 1.5	1.1-2.2			✓	
Seidler[46]	Occup. Case-Con	TCE 2.3 PCE 3.2	1.0-5.3 0.6-16.7	JEM	Exposure: TCE >35 ppm-yrs 2.1 PCE >78.8 ppm-yrs 3.4	1.0-4.8 0.7-17.3	Age, smoking, alcohol		✓	
Spirtas[47]	Occup. Cohort	2.86 F	0.78-7.31	JEM			Age. gender			
USEPA IRIS [48]	Occup. Case-Con + Cohort	1.43	1.13-1.82	JEM Measured Self-reported					Both	✓
USEPA Risk [21]	Occup. Case-Con + Cohort	1.33	0.98-1.8	JEM Measured Self-reported					Both	✓
Wang [49]	Occup. Case-Con	VOC 1.4 F TCE 2.2 F Benzene 1.5 F	1.0-2.0 0.9-5.4 0.9-2.4	JEM			Age, smoking			

F: results specific to females; M: results specific to males
VOC: mixture of volatile organic compounds which can include TCE, PCE, benzene and vinyl chloride

Table II Epidemiological studies showing that TCE and other chemicals cause leukemia										
Adult Leukemia										
Studies	**Type**	**OR, RR, SIR,SMR**	**95% CI**	**Exposure**	**Described threshold**		**Confounder adjustment**	**Dose-duration**	**Incidence vs Death**	**Meta-analysis**
					Exposure or Duration OR	**95% CI**				
Anttila[33]	Occup. Cohort	VOC 1.41 TCE 2.72	0,29-4.12 0.33-9.83	Measured	> 100 µmol/L TCA 2.65	0.72-6.78			✓	
Aschengrau [50]	Environ. Case-Con			Survey JEM	PCE 1.5-80 ppb 7.02	1.5-32.8	Smoking, other solvents		✓	
Bahr[34]	Occup. Cohort	TCE 1.47	0.82-2.43	JEM			Smoking, age, gender			
Bove[36] [36] Marines	Environ. Retro Cohort	VOC 2.33 TCE 1.81 Benzene 1.69	1.08-5.03 0,85-3.85 0.77-3.67	Historical Measures			smoking, race and rank			
Bove [51] Civilians	Environ. Retro Cohort	VOC 1.68 TCE 1.65 PCE 1.82 VC 1.72 Benzene 1.25	0.33-8.67 0.32-8.49 0.36-9.32 0.33-8.83 0.31-5.10	Historical Measures			smoking, race and job			
Bove[37] Incidence	Environ. Retro Cohort	VOC Marines 1.15	0.86-1.55	Historical Measures	> 10 quarters at Camp Lejeune for Marines		Smoking, alcohol, age		✓	
Bove[52] Mortality	Environ. Retro Cohort	VOC Marines 1.13	0.89-1.43	Historical Measures			Smoking, alcohol, age			

Cocco[38]	Occup. Case-Con	3.2	0.6-18	JEM	≤ 5 ppm 1.4	0.3-7.0	age, gender		✓	✓
Cohn[39]	Environ. Cohort			Measured	TCE Acute LL 0.1-5 ppb 1.85 F Chronic LL > 5 ppb 1.57 F Acute ML 0.1-5 ppb 1.23F Chronic ML > 5 ppb 1.79 F PCE Acute LL 0.1-5 ppb 1.89 F	1.03-3.7 0.95-2.6 0.84-1.8 0.9-3.55 1.0-3.44	Age, gender		✓	
Hansen[40]	Occup. Cohort	1.9 M 3.1 F	0.6-4.4 0.04-18	Measured			Age		✓	
Fagliano[53]	Environ.	VOC 1.53 F	1.02-2.21	Measured	VOC 72 µg/L 1.68		Gender		✓	
Hansen [41]	Occup. Cohort	1.19 M	0.72-1.86	Measured			Age		✓	✓
Hadkhale [54]	Occup. Cohort + Case-Con.	Benzene 2.62	1.57-4.39	JEM	<40 ppm-yrs 1.64	1.13-2.39		✓	✓	✓
Raaschou-Nielsen [45]	Occup. Cohort	1.7 F 1.1 M	0.89-2.86 0.84-1.37	JEM					✓	
Childhood Leukemia and non-Hodgkin's Lymphoma (Maternal exposure)										
Costa [55]	Environ. Case-Con	VOC* 5.0	0.75-33.5						✓	
Ruckart [56]	Environ. Cohort				TCE < 2 ppb 1.6 PCE < 44 ppb 1.8 VC < 2 ppb 2.0	0.5-5.4 0.5-6.6 0.5-8.3	Age, smoking		✓	

F: results specific to females; M: results specific to males
VOCs: mixture of volatile organic compounds which can include TCE, PCE, benzene and vinyl chloride

B. Animal Studies

Reporting animal study results: In addition to epidemiological studies, results obtained in animal models that mimic human disease and that demonstrate a role for TCE exposure are included in the causation determinations. Similar to the approach I used for my epidemiological review of TCE I began my evaluation of animal studies by reviewing those identified by the 2017 ATSDR Assessment of the Evidence, included any studies mentioned in the EPA 2020 Risk Evaluation of Trichloroethylene, and supplemented my review with a PubMed-based literature search for individual and review articles.

The ability of TCE to cause lymphomas or leukemias in mice and rats has been studied, albeit more limitedly than it has been studied in humans. One older study reported an increase in leukemia in selected strains of mice and rats treated with high concentrations of TCE by inhalation.[57] A second study found an increase in the incidence of lymphomas in female mice exposed to TCE via inhalation.[58]

C. Mechanism of Action

When available, mechanistic information was included here as part of the causation determinations.

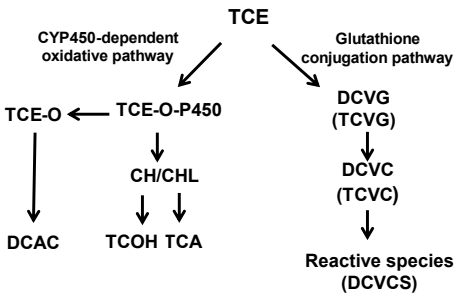
Most if not all of the toxicological effects of TCE require its metabolism.[59] [60] Toxicokinetic data indicate that TCE metabolites are present in both human blood and urine, and have been found in multiple mouse tissues (blood, urine, kidney, liver, bone marrow, and lymphoid tissues) following TCE exposure.[61] Since TCE metabolism is an important part of its toxicity, the discussion of how TCE triggers cancer growth will be preceded by a brief description of TCE metabolism.

1. TCE metabolism

As a small lipophilic (fat soluble) chemical, TCE can easily cross biological membranes regardless of whether exposure occurs through a dermal, oral, or inhalation route. Following its absorption, TCE rapidly partitions into blood by binding to soluble components such as lipids. Once in the bloodstream, TCE is widely distributed throughout the body, but it quickly transitions to the two main sites of metabolism, the liver and the kidney.

In the liver, TCE is subject to oxidative metabolism by cytochrome P450s, most predominantly CYP2E1. The first step in the oxidative metabolism of TCE is the formation of an unstable intermediate (TCE-O-P450) that then leads to the generation of reactive metabolites chloral hydrate (CH) [aka trichloroacetaldehyde hydrate (TCAH)] and chloral (CHL). CH/CHL is reduced by aldehyde dehydrogenases or P450s to trichloroethanol (TCOH) or oxidized to trichloroacetic acid (TCA). Alternatively, TCE-O-P450 can be converted to TCE-epoxide

Figure 1. TCE metabolism



(TCE-O). TCE-O can form dichloroacetyl chloride (DCAC).trichloracetaldehyde) **(Figure 1**).

The secondary pathway for TCE metabolism involves conjugative metabolism with glutathione-S-transferases (GSTs). Conjugation is a process that generally leads to detoxification. However, that is not the case for TCE and many other halogenated compounds, which get converted into harmful reactive metabolites. GSTs conjugates di- and trichlorovinyl-L-glutathione (DCVG and TCVG) are formed in the liver and then transition to the kidney where they are cleaved into di- or trichlorovinyl-L-cysteine (DCVC or TCVC). These products can then be enzymatically converted to the reactive metabolite DCVCS [e.g. N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine) which has been shown to be carcinogenic.

2. TCE genotoxicity

Carcinogenesis is a multistep process that starts with conferring tumor clonality, i.e. the ability of single cells to begin to proliferate abnormally. This transformation is crucial to tumor growth and is quite different from the carefully-controlled and limited proliferation of normal cells. Tumor clonality is thought to require DNA-specific damage known as genotoxicity (which may or may not involve mutagenicity). TCE has been labeled as a genotoxic chemical. While scientific studies have yet to demonstrate a level of TCE exposure below which cancer risk goes to zero, epidemiological studies do provide evidence that TCE, at levels of exposure comparable to and lower than those encountered at Camp Lejeune, can cause cancers, including but not limited to leukemia and NHL. The ability of TCE to cause genotoxicity means that it can initiate the carcinogenic process.

Although it is clear that TCE-induced genotoxicity is important in promoting kidney cancer, the role of TCE-induced genotoxicity in causing hematopoietic cancers has not been as well studied. Nevertheless, there is evidence that *in vitro* exposure to TCE oxidative metabolites causes DNA damage (micronucleus formation and chromosome aberrations) in human lymphocytes. [62]

Sister chromatid exchange was increased in workers chronically exposed to TCE, and in human lymphocytes exposed to TCE oxidative metabolites.[63, 64] Similarly, lymphocytes from workers exposed to TCE demonstrated a highly significant increase in the frequency of chromosomal structural aberrations (breaks, gaps, translocation, deletions, inversions) and hyperdiploid cells.[65] *In vivo* exposure to TCE or benzene in mice similarly caused aneuploidy in lymphoid cells and bone marrow of mice.[66] Lastly, exposure to the toxic metabolite DCVC is toxic to bone marrow in calfs.[67] Taken together, the ability of TCE metabolites from both the oxidative and glutathione pathway to cause DNA damage in mature lymphocytes as well as immature lymphocytes in the bone marrow strongly supports that TCE-induced genotoxicity plays a role in the etiology of NHL and leukemia.

In addition to the scientific evidence that TCE can promote hematopoietic cancer via genotoxicity, there is also evidence that TCE can further support cancer development via immunotoxicity. This mechanism is discussed in Opinion 2.

D. Agency conclusions

Below are the findings of various agencies around the world on the association and causal relationship between TCE and NHL/leukemia. I note that it is standard among scientific experts, including myself, to refer to the reports of these agencies where they are available.

1. NHL

ATSDR: Sufficient evidence for causation. The ATSDR stated that meta-analyses accounting for between-study heterogeneity, influential observations, and data quality consistently indicate positive associations between NHL and exposure to TCE. [23]

USEPA IRIS Toxicological Review of Trichloroethylene (2011): The IRIS report concluded that the human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for NHL. The body of epidemiological evidence on NHL and TCE is comprised of occupational cohort studies, population-based case-control studies, and geographic studies. Most studies reported observed risk estimates for overall TCE exposure. [48]

USEPA Risk Evaluation of Trichloroethylene (2020): The USEPA stated that a new meta-analysis confirmed the conclusions of the 2011 IRIS Toxicological Review of Trichloroethylene. They noted that the human epidemiological database identifies a statistically significant association between TCE exposure and NHL. [21]

International Agency for Research on Cancer (IARC): The IARC stated that a positive association has been observed between exposure to TCE and NHL.[68] TCE was generally categorized by IARC as Group 1 ("carcinogenic to humans") – which is the highest classification given by IARC to a carcinogenic substance.

National Toxicology Program Report on Carcinogens, Fifteenth Edition (2015): "Overall, there is some evidence of an association between exposure to trichloroethylene and NHL based on findings of a modest increase in risk of NHL in several studies with different study designs and in different populations, although the strength of the evidence varied." [69]

2. Leukemia

ATSDR: Equipoise and above evidence for causation for all types of leukemia. [23]

EPA: Trichloroethylene exposure is associated with several types of cancers in humans, especially kidney, liver, cervix, and **lymphatic system**. Animal studies have reported increases in lung, liver, kidney, and testicular tumors and **lymphoma** from inhalation and oral exposures in rats and mice. https://www.epa.gov/sites/default/files/2016-09/documents/trichloroethylene.pdf

A. Summary

1. NHL

Consistent with my opinions on causation, federal agencies agree that epidemiological evidence is sufficient for a causation designation for TCE and NHL. This is based on numerous mid- to high-quality case control and cohort studies, as well as multiple meta-analyses (Table I). This includes studies showing increased incidence of NHL at levels of exposure similar to those found at Camp Lejeune. [36, 37, 39]Supporting evidence in animal models of a direct connection between TCE exposure and NHL was limited, not because studies generated negative results, but because such studies have not been conducted. There is evidence that TCE-induced NHL involves genotoxicity. Plus, that there are clearly demonstrated immunotoxic effects of TCE in both humans (Table III) and animals indicates that

lymphoid cells are a target of TCE toxicity. In my professional opinion, it is more likely than not that a causal relationship exists between TCE exposure and NHL.

2. Leukemia

The association between TCE exposure and leukemia has not been studied as rigorously as the connection to NHL. However, there are a number of epidemiological studies that provide evidence that TCE can cause leukemia at levels of exposure to the chemicals that are similar to those found at Camp Lejeune (Table II).[36, 37, 39, 51, 52] Certainly, there was enough data to convince the ATSDR that there is equipoise and above evidence for causation for all types of leukemia. There are also some, admittedly limited, animal and mechanistic data to support the equipoise designation.

Lymphoid tissue neoplasms arise in the immune system and result from events that occur within immature lymphoid cells in the bone marrow (leukemias), or more mature cells in the peripheral organs (NHL). As such, the distinction between lymphoid leukemia and NHL is largely distributional with overlapping entities, such that a particular lymphoid neoplasm may manifest both lymphomatous and leukemic features during the course of the disease. Thus, the convincing association between TCE exposure and NHL is analogous and therefore supportive of an association between TCE exposure and leukemia.

Taken together, the weight of evidence leads to the conclusion that TCE exposure causes NHL and leukemia.

VII. ROLE OF THE IMMUNE SYSTEM IN MEDIATING HEMATOPOETIC CANCERS

As stated above, the ability of TCE to cause immunotoxicity is also a very important contributor to the development of NHL and Leukemia. Before describing how the immunotoxic effects of TCE can promote tumorigenesis (OPINION 2) the crucial role of the immune system in mediating cancer in general, and hematopoietic cancers specifically, will be summarized.

A. Summary of Immune System

1. Importance of Immune System

The immune system is crucial for fighting infection and preventing cancer. The importance of a correctly working immune system in combating cancer cannot be overstated. Cancer treatment is undergoing a renaissance due to the recent profound clinical successes of tumor immunotherapy. Thus, understanding more about how immune system dysfunction occurs holds incredible promise to advance our ability to fight this disease. The role of TCE exposure in mediating this dysfunction is described in Opinion 2.

2. Summary of the immune system

The immune system is a network of cells and their soluble mediators. The cells of the immune system can be found in circulation as well as in specific immune organs such as the spleen and lymph nodes. Anything that can trigger a response from the cells of the immune system is called an antigen. Most antigens encountered by humans are harmful foreign molecules such as viral proteins, bacterial toxins, and tumor cells.

Similar to a good security system, the immune system is supposed to prevent intruders from accessing your home. The immune system is comprised of both "innate" and "adaptive" components. When the intruders (e.g., cancer cells) trigger your security alarm, the Innate system acts as the first stage of protection (dogs barking) while you wait for the police (adaptive immune response) to arrive. Anything that disrupts either of those protective elements can increase cancer cell access.

The innate immune system is comprised of cells such as macrophages, dendritic cells, neutrophils, and natural killer (NK) cells. These cells are considered somewhat immune non-specific in that they do not have receptors that recognize specific antigens. The cells of the innate immune system travel to the site of injury (e.g., infection or tissue damage) and provide the first line of defense via the production of soluble mediators known as cytokines or chemokines.

The adaptive immune system provides the second and more specific line of defense against antigens. It is comprised primarily of B cells and T cells (which consist of CD4+ T cells and CD8+ T cells). Unlike the cells of the innate immune system, all B cells and T cells have on their surface a unique receptor specific for one particular antigen, such as a specific tumor marker. Antigen-specific B cells and T cells travel to the site of antigen introduction, guided in part by the presence of the innate system soluble mediators. Once B cells interact with their specific antigen, they begin to make antibodies, soluble proteins that bind to and destroy soluble antigens or indirectly act to promote the death of antigen-expressing cells. Antigen-triggered $CD8^+$ T cells, often called cytotoxic T cells, can kill cancer cells expressing tumor antigens or non-cancerous cells infected by intracellular pathogens. Antigen-triggered CD4+ T cells, often called helper T cells, provide crucial support for B cell antibody production. The effector function of activated CD4+ T cells and $CD8^+$ T cells can involve direct cell-to-cell contact or the release of soluble mediators such as cytokines.

B. Immune System and Tumorigenesis

1. Immune surveillance

The innate and adaptive immune systems work together to prevent cancer through a mechanism known as **immune surveillance.** Immune surveillance is an ongoing process by which the immune system surveys the body for tumors and then eliminates them. Once a cell such as a lymphoid cell has been transformed (e.g., by genotoxicity) into a cancer cell and begins proliferating, it often upregulates tumor-specific antigens, making it a target for the immune system. Unfortunately, the targeted anticancer immune response is not always successful. This is due to bidirectional and sometimes flawed interactions between the immune system and cancer cells known as **cancer immunoediting**. During cancer immunoediting, the host immune system shapes tumor growth in three phases: elimination, equilibrium, and escape.

(a) Elimination

In the elimination phase, proliferating cancer cells expressing tumor antigens are destroyed by a competent immune system. This represents a coordinated attack by the innate and adaptive immune system against cells expressing tumor antigens. The cells of the innate immune system can kill tumor cells through the release of soluble mediators (e.g., perforin and granzyme). The adaptive immune response can cause tumor-cell killing directly through $CD8^+$ T cell cytotoxic mechanisms, indirectly

through different CD4+ T cell-mediated mechanisms, or via the generation of natural antitumor antibodies.

(b) Equilibrium

If not all tumor cells are destroyed during the elimination phase of cancer immunoediting, tumorigenesis may enter into the equilibrium phase. In this phase, the immune system prevents tumor outgrowth but cannot eliminate all tumor cells. Unfortunately, the selective pressure to evade elimination by the activated immune cells can eventually drive the tumor cells to evolve through mutations or epigenetic alterations into cells with mechanisms that allow them to circumvent immune system control.

(c) Escape

The escape phase represents the final phase of tumorigenesis where the tumor cells that have developed to evade the immune system grow progressively and develop into a clinically apparent disease. This involves the establishment of an immunosuppressive microenvironment in the tumor that discourages further destruction by CD4+ and CD8+ T cells.

2. How immune surveillance goes wrong during development of NHL and leukemia

(a) Chronic inflammation

In order for the immune system to work correctly to fight infection or prevent cancer, the innate and adaptive immune systems must maintain a delicate balance between immune activation and deactivation. Temporary inflammation is a crucial part of the immune response to antigens and subsequent tissue repair. The immune response is supposed to be proportional to the threat and will subside once the threat has been resolved. However, when the immune response is not resolved (e.g., cancer is not eliminated), or when the innate immune system is artificially stimulated by extrinsic factors, it can lead to a sustained state of **chronic inflammation** that is more harmful than protective. Chronic inflammation has been shown to be a contributing factor to cardiovascular disease, diabetes, other metabolic diseases, chronic kidney disease, neurodegenerative disorders, and cancer (including leukemias and lymphomas).[70]

Chronic inflammation is an important component of hematopoietic cancers and provides support for tumor progression, metastasis, and anticancer resistance.[71, 72] Inflammation in cancer development is mediated in large part by soluble factors such as IL-6, IL-1β, and TNF-α. Increased levels of IL-6 and TNF-α have been found in the blood and cancer cells from patients with chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML).[73-75] And a meta-analysis showed that elevated circulating levels of TNF-α were consistently associated with an increased risk of NHL. [72] Since cytokines such as IL-6 have multiple functions, some of which are beneficial, the cumulative effect of suppressing them can be problematic. However, studies have shown that IL-6 depletion can block the progression of leukemia [76], while exposures that increase the expression of IL-6 trigger leukemia.[77]

The ability of TCE to increase the levels of pro-inflammatory pro-tumorigenic cytokines will be described in Opinion 2.

Another major player in the inflammatory response to cancer is the cytokine IFN-γ. IFN-γ is a pleiotropic cytokine that is primarily secreted by CD4+ T cells and CD8+ T cells. Aside from its role in promoting proliferation and differentiation of immune cells, IFN-γ has many antitumor effects. It can: (a) act as a cytotoxic cytokine that initiates tumor cell death, (b) increases the ability of macrophages and dendritic cells to activate antitumor T cells, and (c) inhibits the angiogenesis needed for tumor growth.[78] [79] [80] On the other hand, the expression of IFN-γ early in tumorigenesis can promote tumor growth.[78] IFN-γ treatments in patients with hemopoietic cancers has revealed the powerful, albeit dichotomous, nature of IFN-γ resulting in both pro- and anti-tumorigenic effects.[81-83] Reconciling the pro- and anti-tumorigenic effects of IFN-γ is of great interest since the cytokine seems to serve as a nexus for responsiveness cancer immunotherapy. The different tumorigenic effects of IFN-g may depend on concentration, stage of cancer progression, and the presence of cells and/or other soluble mediators that counteract or enhance the effects of IFN-γ. In any case, IFN-γ is a major player in cancer regulation. The ability of TCE to alter levels of IFN-γ will be discussed in Opinion 2.

Closely related to inflammation is oxidative stress, which can be either causal or secondary to inflammation. Oxidative stress also plays a major role in cancer development where it can promote initiation, angiogenesis, invasiveness, and metastasis.[84] This is certainly true for leukemia, in which oxidative stress promotes the occurrence, development, treatment, and prognosis of leukemia.[85] The ability of TCE to increase oxidative stress is discussed in Opinion 3.

(b) Immunosuppression of adaptive immune response

As mentioned above, different forms of immunodeficiency are important risk factors for hematopoietic cancer. However, regardless of whether the patient starts with baseline immunodeficiency, they acquire it during disease progression. Patients with NHL have antitumor T cells that demonstrate suppression and exhaustion and are unable to eradicate lymphoma cells.[86] Leukemia is also associated with suppression of antitumor-specific T cells.[87-89]

The importance of a fully functioning immune system to combat hematopoietic diseases is underscored by the fact that many of the immunotherapies currently being tested are focused on (i) blocking the ability of tumor cells to suppress tumor-specific T cells, and (ii) stimulation of sub-optimally activated T cells. [90] Along these lines, certain types of lymphoma and leukemia are currently being effectively treated with drugs known as immune checkpoint inhibitors, e.g., antiPD-1 and/or anti-CTLA-4 antibodies.[91-93] These antibody treatments block the ability of tumor cells to suppress T cell activity.

As described in Opinion 2 extrinsic factors such as TCE that inhibit the number or activity of CD4+ T cells and/or CD8+ T cells (similar to tumor checkpoint control) promote the development of NHL and leukemia.

VIII. OPINION 2. TCE MORE LIKELY THAN NOT CAUSES IMMUNOTOXICITY THAT CAN PROMOTE NHL AND LEUKEMIA

A. Epidemiological Studies

Table III lists the epidemiological studies that have examined the association between TCE exposure, immunosuppression, and inflammation. These were cross-sectional studies, some of which compared TCE-exposed workers to unexposed workers, and some of which compared unexposed workers to those

diagnosed with TCE-induced hypersensitivity disease. The studies evaluated a variety of immunological endpoints best represented as specific values, such as the mg/ml level of serum immunoglobulin or percentages of specific cell types. Consequently, the data was not presented as Odds Ratios, which is better suited to comparing yes/no disease incidence in two or more populations. In some cases, the endpoints in a published study were presented as bar graphs or as box-and-whisker plots. This is not unusual for this kind of data but necessitated describing the relative differences between controls and TCE-exposed rather than presenting actual number values.

Table II. Epidemiological studies examining TCE exposure and immunotoxicity

Study	Endpoints	TCE exposure estimates (ppm)			Other
		Controls <0.03	<12 (mean=5.2)	>12 (mean=38.4)	
Lan [94]		**Per ml blood**	**Per ml blood**	**Per ml blood**	N=80 Exposed, N=96 Controls
	Total T cells	1356±374	1310±391	**1124±346 (p=0.0001)**	
	CD4+ T cells	675±200	664±220	**577±192 (p =0.004)**	Only selected workers from factories that used TCE but had no or negligible levels of other chlorinated solvents
	CD8+ T cells	544±216	508±175	**430±150 (p=0.007)**	
	B cells	227±133	194±99	**152±68.**1 **(p=0.001)**	
	NK cells	467±279	370±148	**282±145 (p=0.002)**	
Hosgood[95]		**Per ml blood**	**Per ml blood**	**Per ml blood**	
	Effector memory CD4+T cells	225±93	**183±55 (p=0.014)**	**184±89 (p=0.001)**	Same cohort as Lan
	Naïve CD4+ T cells	283±126	293±142	**236±113 (p=0.017)**	

	Naïve CD8+ T cells	216±117	212±101	**152±93 (p=0.0001)**	
Lee [96]		**mg/ml**	**mg/ml**	**mg/ml**	Same cohort as Lan
	Serum IgG	10.99±2.97	**9.24±1.66 (p=0.008)**	**8.9±2.15 (p=0.002)**	
	Serum IgM	1.18±0.820.	**0.76±0.34 (p=0.0008)**	**0.71±0.37 (p=0.002)**	
	Effector memory CD4+T cells	10^3 cells/ml blood 224.9 ± 92.9	10^3 cells/ml blood **181.8** ± 56.7 **(p=0.042)**	10^3 cells/ml blood 184.5 ± 86.1	
Zhang[97]	Serum IgG	N/A	**Decreased**	**Decreased**	Box and whisker plots; no values, but indication of statistical significance
	Serum IgM	N/A	**Decreased**	**Decreased**	
		Controls	**TCE-induced disease**		
Li [98] Compared patients with TCE-induced hypersensitivity to controls with no disease or exposure		**10^9/L**	**10^9/L**		**Saw clearly doubled increase in TNF-α - producing CD4+ T cells: just bar graphs, no values.**
	Neutrophils	3.53±1.08	**7.75±6.8 (p=0.021)**		
	Eosinophils	1.1±1.7	**0.14±0.19 (p=0.013)**		
	Basophils	0.18±0.21	**0.02±0.01 (p=0.002**		
Kamijima [99] Compared patients with TCE-		% more than 3 SD above mean control values	% more than 3 SD above mean control values		N=28 with disease, N=48 Controls Measured end of shift TCA levels, but no
	Serum levels of TNF-α	4%	**79% (p=0.01)**		

induced hypersensitivity to controls				estimates for TCE
Jia [100]	Serum levels of: IL-1β TNF-α IL-6			**Significantly increased serum levels of all three cytokines represented as bar graphs and dot plots**

Bolded values are significantly different from controls. P-values were provided for these values.

The epidemiological studies described how TCE exposure generated immune suppression as indicated by (a) decreased serum levels of IgG and IgM, and (b) decreased blood levels of lymphoid populations including CD4+ T cells, CD8+ T cells, B cells, and NK cells. Aside from markers of immune suppression, indications of inflammation, such as significantly increased levels of TNF-α, IL-1β and IL-6, were found in workers exposed to TCE.

Although there are some differences, mice and humans share many components of the immune system, and mouse models have enabled breakthroughs in our understanding of the human immune system. Consequently, the results obtained from TCE-exposed mice are expected to be relevant to human exposure. Inhalation exposure to TCE in mice enhanced susceptibility to pulmonary infection, an appropriate endpoint for immune suppression.[101] Similarly, mice exposed to TCE in drinking water showed significantly decreased cell-mediated immunity and bone marrow stem cell colonization. [102] High-dose exposure to TCE for 4 weeks caused a 70% decrease in antigen-induced antibody production in Sprague-Dawley rats. [103]

Although TCE can cause immunosuppression in animal models, it can also cause inflammation. Mice sensitized to dermal TCE exposure showed dramatic increases in the levels of IL-6, IL-1β, and TNF-α in the kidney. [104] The functional significance of these TCE-induced inflammatory mediators was evident when a TNF-α inhibitor was shown to relieve liver damage in TCE exposed mice.[105]

Similar to findings in humans, studies in animal models have shown that TCE can alter the number, function, and/or phenotype of lymphoid cell populations in the blood, spleen, and thymus. [102, 103, 106]

As mentioned above, the cytokine IFN-γ has an outsized role in determining tumor progression and regression.[78] My lab has shown that TCE exposure in mice alters IFN-γ production at the level of protein production, gene expression, and epigenetic alterations.[10, 11, 13] TCE-induced alterations in IFN-γ production represent another mechanism by which TCE can promote carcinogenicity.

Lastly, aside from its ability to cause hypoactivity of the adaptive immune response as shown in Table III, TCE can in some cases cause hyperactivity of the adaptive immune response. As myself and others have shown, TCE exposure can promote hypersensitivity and increased T cell and B cell function in humans and animal models.[15, 17, 106-110] These studies provide additional evidence of TCE-induced immune dysfunction.

C. Mechanism of Action

The function of immune cells, similar to almost all cells, is largely mediated via gene expression. Researchers, including myself, have shown that TCE-induced changes in IFN-γ levels reflect a corresponding change in expression of *ifng*. [13, 111] My research team has linked the TCE-induced change in gene expression to at least two mechanisms: (a) binding to T cell proteins in a way that triggers transcription factor activation and downstream gene expression, and (b) inducing long-term epigenetic alterations that help control gene expression.[7, 9 10 1, 11, 12] Both of these TCE mechanisms have subsequently been confirmed in humans. [112, 113, 114, 115]

The fact that TCE generates epigenetic alterations in both humans and animal models provides a mechanism to explain why TCE effects can remain even after exposure cessation.[2] Along these lines, occupational TCE exposure was found to increase aging in terms of epigenetic alterations in lymphocytes by two years compared to chronological aging. [116]

D. Federal and International Agency Conclusions

USEPA Risk Evaluation of Trichloroethylene (2020): "Overall, immunotoxicity in the form of both autoimmunity and immunosuppression following TCE exposure are supported by the weight of evidence." The regulatory values derived from a mouse study of immunosuppression[101] were used by the EPA to evaluate the potential risk to workers by TCE exposure**.**[21]

E. Summary

TCE has been shown to alter several immune parameters in humans and animal models. This provides biological plausibility to my opinion that more likely than not exposure to TCE causes NHL and leukemia. These alterations are clear indications of immunotoxicity. There are studies in animal models that confirm TCE-induced immunosuppression, and potential mechanisms have been described that provide biological plausibility. Since both immunosuppression and inflammation are crucial mediators of hematopoietic cancers, TCE-induced immunotoxicity that encompasses both processes more likely than not promotes the development of both leukemias and NHL.

It is my opinion that TCE-induced immunotoxicity would occur at the monthly median levels of TCE contamination found in the water at Camp Lejeune. The EPA has designated the immune system as the most sensitive non-cancer endpoint as evidenced by their focus on immune system endpoints for the derivation of regulatory values.[21] In mouse models levels of TCE below that of occupational exposure cause functional immune system disruption.[2] Similarly, workers exposed to TCE as low as between 0-2.5 ppm 8-hr TWA (compared to OSHA PEL of 100 ppm 8-hr TWA) demonstrated immune dysfunction as indicated by increased levels of autoantibodies.[117] This strongly suggests that the TCE exposure at Camp Lejeune was sufficient to trigger immunotoxicity that promoted development of NHL and leukemia.

IX. OPINION 3. TCE-INDUCED OXIDATIVE STRESS CAN AUGMENT IMMUNOTOXICTY IN PROMOTING NHL AND LEUKEMIA

A. Background

In addition to inducing immune system changes that can promote tumorigenesis, TCE can also enhance cancer development by increasing oxidative stress.

Oxidative stress is considered the cellular imbalance between antioxidants and oxidants [reactive oxygen species (ROS)]. ROS are a byproduct of mitochondrial respiration during normal cell function and can serve as important signaling molecules in normal physiology. Cells have a protective system mediated by antioxidants designed to keep ROS at physiologically normal levels. However, an imbalance between the formation and destruction of ROS can occur leading to excess intracellular accumulation of ROS, a condition known as oxidative stress.

The excess ROS associated with oxidative stress can cause cell damage through harmful reactions with proteins, lipids and DNA. It is therefore not surprising that oxidative stress is a causative factor for multiple diseases.[118] This is at least due, in part to its ability to promote chronic inflammation. [118, 119]

Although the role of oxidative stress in later stages of tumorigenesis is complicated, its ability to augment inflammation during the initial stages of cancer development gives it a clearcut role in early tumorigenesis. Oxidative stress has been implicated as an intermediate in DCVC-induced DNA damage following TCE exposure.[120] Aside from promoting cell transformation, reaction oxygen species can also promote tumor development by suppressing tumor-specific T cells.[121]

ROS in the tumor microenvironment can be derived from the tumor cells and/or from cells of the innate immune system, such as macrophages, which are recruited to the tumor site.

B. TCE-induced oxidative stress

An exposure-dependent association between TCE exposure and systemic markers of oxidative stress has been reported in a mouse model.[122]

Indicators of oxidative stress in TCE-exposed mice include increased levels of lipid peroxidation-derived aldehydes such as malondialdehyde, and higher serum iNOS and nitrotyrosine.[123] It is still not clear how TCE increases oxidative stress. However, signs of oxidative stress have been found in liver[124], placenta[125], gut[126], embryonic heart[127], and kidney [128] and spleen[129] following TCE exposure. Thus far, TCE-induced oxidative stress has been associated with kidney damage [128], skin hypersensitivity [130], functional neurotoxicity [131], autoimmune disease[132], liver cancer[133], and hematological cancers.[134]

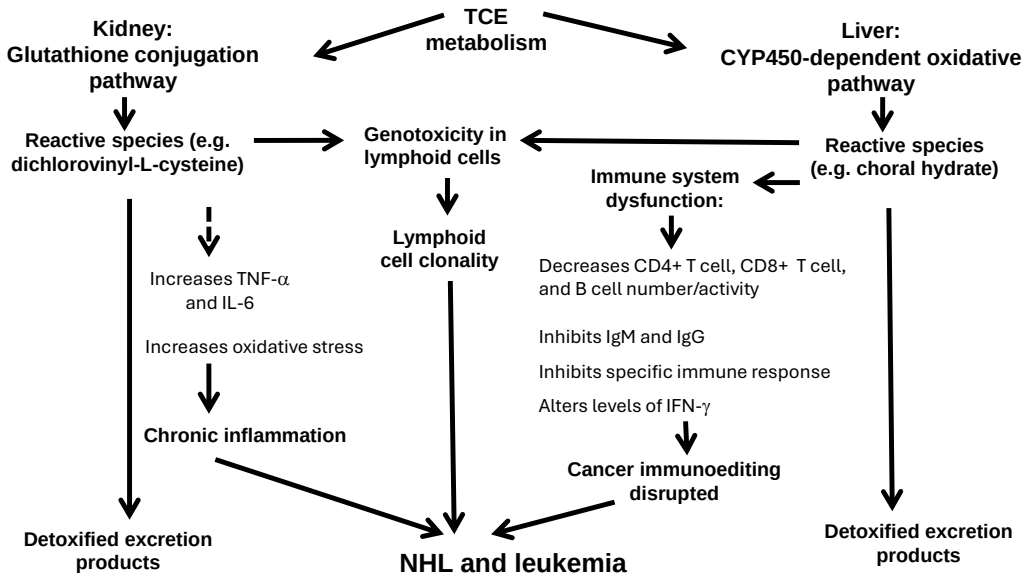
Oxidative stress is not just a by-product of TCE exposure; it appears to be important in mediating TCE toxicity. This has been demonstrated by showing that antioxidant treatments protect against cardiac toxicity, dermal hypersensitivity, and autoimmunity caused by TCE exposure. [132, 135, 136] Making the same point was the finding that the absence of antioxidant activity exacerbates TCE-induced neurotoxicity.[137] Although the role of TCE-induced hematopoietic cancers and oxidative stress has not specifically been evaluated, DNA damage mediated by TCE-induced oxidative stress has been reported as a mechanism for TCE genotoxicity in liver cells.[100] Since the genotoxicity of oxidative stress does not appear to be cell

specific, it is more likely than not that the oxidative stress induced by TCE could cause genotoxicity in lymphoid cells.

C. Summary

Oxidative stress and chronic inflammation are important components in the development of several types of cancer, including NHL and leukemia. TCE increases oxidative stress in many organ systems, including the lymphoid. Thus, it is more likely than not that TCE-induced oxidative stress, together with TCE-induced genotoxicity, inflammation, and immunosuppression, comprises a multi-component mechanism by which TCE causes hematopoietic cancers (Figure 2).

Figure 2. Model explaining how TCE causes NHL and leukemia



X. OPINION 4. TCE LEVELS AT CAMP LEJEUNE WERE HAZARDOUS TO HUMAN HEALTH

When assessing the likelihood that a toxicant causes pathology, duration, temporality, and concentration are usually considered. These will be addressed here regarding the Camp Lejeune plaintiffs.

A. TCE levels at Camp Lejeune

The ATSDR reconstructed the VOC concentrations in the drinking water at Camp Lejeune.[116] The agency reported the levels of TCE at the Hadnot Point water treatment plant reached an estimated maximum average of 783 mg/L, compared to a maximum measured value of 1,400 mg/L, during the time period between August 1953 and December 1984. The Holcomb Boulevard water-distribution contained estimated maximum concentrations of TCE of 32 mg/L prior to 1972, and an estimated maximum concentration of 66 mg/L between 1972 and 1985. Levels of PCE at the Tarawa Terrace water treatment plant reached an estimated maximum level of 215 mg/L, and a maximum monthly average level of 183

mg/L, and exceeded the EPA MCL (5 mg/L) from November 1957 and February 1987. These levels of TCE and PCE in the drinking water were hazardous to human health and are known to cause kidney cancer.

I have also reviewed the ATSDR water modeling reports that are publicly available and the summary tables of Plaintiff's expert Morris Maslia. These levels shown to be present at Camp Lejeune are hazardous to humans generally and are known to cause kidney cancer.

B. TCE exposure duration

As mentioned earlier, the ATSDR conducted a comprehensive examination of mortality causes in Marines and non-service personnel stationed at Camp Lejeune during the years between 1975-1985. [23, 36, 51] The ATSDR found sufficient evidence for causation regarding TCE and NHL, and equipoise and above evidence for causation regarding TCE and leukemias.[23] Marines in the mortality studies served an average of 18 months on the base. The non-military personnel worked at the base for an average of 29 months.

Although the ATSDR did not study the exposure duration required to cause disease, they did say that epidemiological data did not contradict a minimum duration of 30 days.[23] They went on to say; "Moreover the results from the Camp Lejeune mortality studies suggest that a 30 day minimum duration requirement may be appropriate since the elevated risks for some of the disease evaluated were observed for exposure durations of 1-3 month."

A recent evaluation of the Camp Lejeune data similarly concluded that based on the concentrations of contaminants at the base, just one month of exposure was sufficient to increase the likelihood of developing cancer.[138]

All of the plaintiffs in this case were on base at Camp Lejeune for one month or longer than one month during the exposure period.

C. TCE disease latency

When evaluating causality, the time between exposure and the onset of disease is another factor to consider. A long-term cohort cancer incidence study by Bove *et al*. compared Marines and civilians who had lived at Camp Lejeune with those that had lived at Camp Pendelton that did not have contaminated drinking water.[37] Marines stationed at Camp Lejeune had an increased incidence of leukemia (OR 1.15; 95% CI 0.86-1.55) while civilians living at Camp Lejeune had increased incidence of NHL (OR 1.31; 95% CI 0.84-2.03). When discussing the limitations of the ATSDR's 2024 examination of cancer incidence among Camp Lejeune personnel, Dr. Bove noted that the median age of personnel at the end of the follow-up examination was only 57 years.[37] Dr. Bove went on to note that for the cancers that have been associated with occupational TCE exposure such as NHL, and cancers of the kidney and liver, the median ages at diagnosis are 67, 64 and 65 years, respectively. Thus, it is likely that the cancer incidence of the people exposed to TCE at Camp Lejeune would have increased if the follow-up had been extended.

D. TCE exposure level

There is no single methodology that clearly defines what concentration of TCE causes NHL or leukemia. However, a combined WOE approach can nevertheless demonstrate levels that have been shown to be hazardous to human beings generally and are known to cause NHL and Leukemia.

The epidemiological studies in Tables I and II provide evidence that TCE and other VOC cause NHL or leukemia under the conditions found at Camp Lejeune. However, using these studies to define the precise minimum exposure or precise minimum duration to cause hematopoietic cancers is challenging. Exposure-duration studies conducted to assess hazards are confined to drug clinical trials. It would be unethical to conduct similar studies using known toxicants. Some of the epidemiological studies in Tables I and II compared results from TCE-exposed to non-TCE exposed without attempting to define exposure levels. Some devised relative exposure classifications (e.g. low, medium, high) without defining specific concentrations. However, there have been some epidemiological studies that did describe specific exposure levels. In one such study, which like Camp Lejeune, involved water contamination with both TCE and PCE, increased NHL incidence was associated with levels of TCE exposure as low as < 5 ppb, or levels of PCE at > 5 ppb.[39] The same study showed an increased incidence of acute lymphocytic leukemia (ALL) at exposure levels of TCE or PCE at < 5ppb, and increased incidence of chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia at levels of TCE exposure at >5 ppb, and acute myeloid leukemia (AML) at levels of TCE < 5 ppb. Another study showed that combined childhood leukemia and NHL cases were increased by exposure to TCE < 2 ppb, PCE < 44 ppb, and vinyl chloride at < 2 ppb.[56]

Using epidemiological studies to define a hazard "threshold" would not be possible without controlled experiments in humans; without such evidence application of existing epidemiological studies underestimates the lowest numbers hazardous to human beings and that cause NHL and Leukemia because it is probable that there is risk at levels below those estimated in an epidemiological study. Epidemiology, however, is generally considered to be the best evidence of these exposure levels being hazardous to humans generally and known to cause NHL and Leukemia. If these studies exist they should be utilized first in this analysis, as I have done in this report.

A second potential way to discuss the relationship between exposure levels and increased NHL and leukemia incidence involves the use of regulatory values such as the oral slope factor. While not directly related to causality, such data points can be referenced in an overall evaluation of the likelihood that a particular exposure caused a disease outcome. Regulatory values are derived by the EPA based on cumulative exposure-response data from epidemiological and animal studies. They are designed to estimate future risk from a chemical in order to inform mitigation decisions. Of course, using estimates of future risk does not fit an analysis for determining causation for individuals who already have cancer because the risk of someone who has cancer getting cancer is of course 100%. However, when kept in proper context, these values can be referenced to discuss whether a known chemical exposure could be expected to increase the incidence of a specific pathology.

Predictions based on oral slope factors probably underestimate cancer risk since real accuracy would require defining the full level of exposure (e.g. involving multiple routes of exposure) and the additive effects of coexposure to other chemicals with their own slope factors. However, even if we did not have the data clearly showing an increase in hematopoietic cancer incidence at Camp Lejeune, the oral slope factor would predict such an increase. Thus, considering both methodologies, and understanding the limitations of the oral slope factor and risk assessment in this situation it is reasonable to focus on the epidemiological data first and then consider whether a risk assessment analysis is consistent.

There have been several attempts to use cancer slope factors generally to assess the drinking water at Camp Lejeune. The ATSDR in its public health assessment in 2017 looked at risk assessments generally when conducting its analysis. The ATSDR data in this regard confirms that the levels of the toxins in the

water at Camp Lejeune are hazardous to humans generally and based on the oral slope factors would be expected to increase cancer incidence.

Second, the oral cancer slope factor is expressed in mg/kg/day and is used to predict additional cases of cancer per million people exposed to a particular concentration of a chemical for a lifetime. The TCE oral slope factor specific is 4.6 x 10^{-2} mg/kg/day. Active military personnel are estimated to ingest from 4 to 10 L/day depending on temperature and activity level and to weigh a default 80 kg.[5] As mentioned above, amounts of TCE ingested from drinking water need to be at least doubled to factor in dermal and inhalation exposure routes to calculate total exposure.

To estimate the increased cancer risk from chemical exposure, the oral cancer slope factor for a specific chemical is multiplied by the lifetime exposure (in mg/kg/day). An example of its use will be provided here using TCE levels of 783 μg/L which represent the maximum monthly average of TCE found in the drinking water at Hadnot Point.[139] Using default values of 4- 10 L/day of water a Marine's exposure to TCE would be between 0.078 mg/kg/day (0.783 mg/L x 2 (accounting for dermal and inhalation x 4 liters/day/80 kg) to 0.196 mg/kg/day (0.783 mg/L x 2 (accounting for dermal and inhalation x 10 liters/day/80 kg). If you multiply that by the oral slope factor for TCE (0.046 per mg/kg/day) you would predict at least between 3,588 and 9,016 extra cancers per million people for individuals chronically exposed to that level of TCE. A more accurate analysis would need to adjust for the duration of exposure and use a more specific estimate of the contribution from dermal and inhalation exposure. In addition, these values are for TCE alone and do not take into account coexposure effects from the other contaminants. These values are also limited to adult exposure. According to the ATSDR children between the ages of 0-3 years old who lived on the base for 3 years were predicted to experience at least 4,500 extra cancers per million people from the cumulative chemical exposure. https://stacks.cdc.gov/view/cdc/43951

A third way to get perspective on TCE exposure levels and pathology involves the new Existing Chemical Exposure Limit (ECEL) for TCE proposed by the EPA on October 31,2023. The ECEL was published in the Federal Register as a proposed rule concerning *Trichloroethylene: Regulation Under the Toxic Substances Control Act*.[6] The EPA is proposing a new ECEL for TCE of either 4.0 ppb or 1.1 ppb for occupational inhalation exposures as an 8-hour time-weighted average (TWA). Only exposures equal to or below the ECELs are considered free from an unreasonable risk for chronic cancer and non-cancer and acute non-cancer inhalation endpoints.

The proposed 1.1 ppb (0.0059 mg/m^3) ECEL is approximately 100,000 times lower than the OSHA PEL of 100 ppm for an 8-hour TWA. This reflects the EPA's commitment to using recent advances in modeling and scientific interpretation of toxicological data to devise new regulatory guidelines for environmental hazards.

Using the default air intake values (15.2 m^3/day for adult males) provided by the ATSDR[7] it is possible to estimate TCE exposure based on the ECEL of 0.00037 mg/kg/day for an 8-hour day. [15.2 m^3/day divided by 24 hours = 0.63 m^3 air intake per hour; 0.63 m^3 air/hour x 0.0059 mg/m^3 = 0.0037 mg/hour x 8

[5] *See* https://www.epa. gov/sites/default/files/2015-11/documents/OSWER-Directive-9200-1-120-ExposureFactors.pdf.
[6] *See* https://www.govinfo.gov/content/pkg/FR-2023-10-31/pdf/2023-23010.pdf.
[7] *See* https://www.atsdr.cdc.gov/hac/phamanual/appg.html.

hours/80 kg = **0.00037 mg/kg/day**]. In contrast, a marine's exposure to 783 µg/L TCE in Camp Lejeune drinking water with a 4 L ingestion rate/80 kg = **0.039 mg/kg/day**. Thus, even with a conservative drinking water rate of 4 L/day, the Marine at Camp Lejeune would have been exposed on a daily basis to a level of TCE almost 100-times higher than the level thought not to be unsafe. This level of TCE exposure would need to be adjusted upward to reflect inhalation and dermal exposure.

E. Summary

Taking into account disease latency, exposure levels and exposure duration it is more likely than the TCE exposure at Camp Lejeune was hazardous to human health and sufficient to promote the development of NHL and leukemia.

XI. OPINION 5. TCE-INDUCED NHL AND LEUKEMIA IN THE PLAINTIFFS WAS AUGMENTED BY AGGREGATE EXPOSURE VIA INHALATION AND DERMAL ROUTES, AND BY CUMULATIVE COEXPOSURE TO OTHER CONTAMINANTS IN THE DRINKING WATER

There is considerable evidence that the toxic response to a chemical such as TCE by one route of exposure can be augmented by exposure to the same chemical by a different route of exposure or by coexposure to another chemical. This is an important consideration since cumulative and aggregate exposure assessments more realistically depict real-world exposures in both occupational and environmental settings. This is certainly true at Camp Lejeune where there were several chemicals of concern in addition to TCE and the Marines and civilian workers at Camp Lejeune experienced multiple pathways of exposure to the contaminated water. Aggregate exposure assessments are used when an individual is exposed to a single contaminant via different routes. Cumulative exposure assessments consider the hazards posed by multiple toxicants.

A. Aggregate exposure to TCE

On April 18, 2024, Michal Freedhoff, the EPA Assistant Administrator for the Office of Chemical Safety and Pollution Prevention, signed the following document: Action: Final Rule Title: Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA).[8] In this document, the EPA noted that the inclusion of all exposure pathways relevant to the chemical substance should be taken into account when assessing its effects on human health. TSCA is designed to assess the hazards posed by occupational and consumer exposures. The same principle also holds true for human environmental exposure.

At Camp Lejeune, hazard assessment has focused on TCE exposure from ingesting contaminated drinking water. However, when estimating the hazards posed by TCE, which is a volatile organic compound, it is important to also consider inhalation and dermal exposures resulting from the use of and exposure to the TCE-containing drinking water for cleaning, bathing, cooking and other daily activities. Results from PBPK modeling and from human experimental samples have shown that inhalation and dermal exposure from TCE-contaminated water is at least equal to that from ingestion.[140, 141] A 2024 study used new methodology to quantify cancer risk for the Marines who had lived at

[8] *See* https://www.epa.gov/system/files/documents/2024-04/prepubcopy_frl-8529-02-ocspp_fr_doc_aa_esignature_verified.pdf.

Camp Lejeune between 1953 and 1986.[138] They estimated that most of the increased cancer risk (59%) was due to inhalation from the contaminated water, while ingestion and dermal exposure contributed 34% and 5.5% respectively. They concluded that the inhalation exposure pathway posed about 1.7 times greater risk than the ingestion pathway. This suggests that, at the very least, one should double the ingestion exposure of TCE to estimate total TCE exposure at Camp Lejeune.

Breathing indoor air contaminants in Camp Lejeune's buildings due to vapor intrusion is another potential pathway of exposure. Volatile chemicals such as TCE in contaminated shallow groundwater can evaporate and move upward through the ground surface into indoor air of overlying buildings—this process is called vapor intrusion. At this time, ATSDR is evaluating about 150 buildings at Camp Lejeune for vapor intrusion.[9] Although the values obtained will reflect current rather than historical levels of TCE in groundwater, they may show many decades later that his exposure still is present and inform the contribution that this exposure pathway has to total exposure.

B. Cumulative coexposure to TCE and other contaminants

There is scientific support that coexposure to one or more chemicals with additive or synergistic effects likely promotes disease at concentrations that would be less harmful for any of the chemicals alone. However, few epidemiological studies have yet been done to quantify those additive or synergistic effects.

Underscoring their practice of considering additivity when chemicals target the same endpoint, the EPA is developing improved methods for assessing health risks from environmental chemical mixtures. https://assessments.epa.gov/risk/document/&deid=359745

The ATSDR is similarly committed to better defining the impacts of chemical mixtures.[10] To carry out this legislative mandate, the ATSDR's Division of Toxicology has developed and coordinated a mixtures program that includes *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity.[11] The ATSDR has identified 16 Final or Draft Interaction Profiles describing chemical mixtures of human health concerns. Four of the Interaction Profiles contain TCE. One of these four mixtures contains TCE and PCE, and the other contains TCE and vinyl chloride. The study of toxic coexposures is still relatively new. However, I, as well as others, have demonstrated that coexposure can augment TCE-induced toxicity and gene expression.[18, 34, 142] Although these studies did not examine TCE in combination with PCE, benzene, or vinyl chloride, they provide proof of concept that coexposure effects should be considered when assessing the hazards posed by TCE exposure.

A quantitative evaluation of the coexposure effects posed by the chemicals in the water at Camp Lejeune on the incidence of NHL and leukemia is beyond the scope of this report. However, it should be

[9] *See* https://www.atsdr.cdc.gov/ sites/lejeune/Vapor-Intrusion-PHA.html.
[10] *See* https://www.atsdr.cdc.gov/mixtures/assessment.html.
[11] *See* (https://www.atsdr. cdc.gov/interactionprofiles/ip02.html).

noted that the chemicals share several structural and functional similarities that make it likely that additive effects from coexposure occurred.

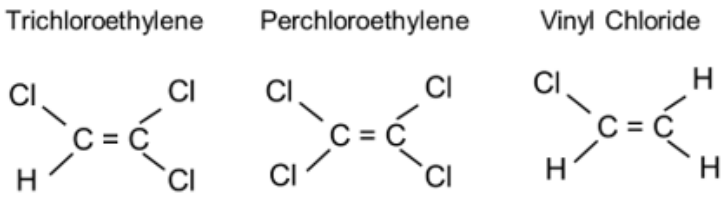


Figure 3. Structure of TCE, PCE and vinyl chloride

Three of the chemicals are structurally similar. TCE, PCE, and vinyl chloride all contain 2 carbon molecules with three, four, or one chloride molecules respectively (**Figure 3**).

There are also several functional similarities among TCE, PCE, benzene, and vinyl chloride. They have qualitatively similar metabolic pathways in both rodents and humans.[143] This includes oxidative metabolism in the liver and conjugative metabolism in the kidney, although there are some quantitative differences in the metabolites formed. Oxidative metabolism of TCE, PCE, vinyl chloride, and benzene is largely, but not solely dependent on the same enzyme, CYP2E1.[144] All four chemicals are converted into toxic and reactive metabolites that have been linked to cancer in epidemiological studies, including hematopoietic cancers. [36, 51, 145]

Taken together, it is more likely than not that exposure to three known carcinogens (TCE, benzene, and vinyl chloride) and one likely carcinogen (PCE) would have an additive effect on tumorigenicity. Rosenfeld *et al.* examined the combined cancer risk from coexposure to the different contaminants in the drinking water at Camp Lejeune. [138] They predicted that the cancer risk from TCE exposure would be increased by coexposure to other contaminants at Camp Lejeune.

C. Overall Summary for Opinion 5

Estimating hematopoietic cancer risk for the Marines at Camp Lejeune cannot be based solely on drinking water ingestion of TCE. It should also take into account inhalation and dermal exposure from the contaminated drinking water, and perhaps inhalation of indoor air contaminated by vapor intrusion. The likely additive effects of coexposure to multiple carcinogens, TCE, vinyl chloride, benzene, and probably PCE should also be taken into account.

Signature. I hold all of the above opinions to a reasonable degree of scientific certainty. I reserve the right to supplement and/or review my opinions as presented in this report as new information becomes available.

12-4-14

Kathleen M. Gilbert, PhD Date

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Appendix A

KATHLEEN M. GILBERT, PHD
IMMUNOTOXICOLOGIST

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SUMMARY: Although initially trained as a molecular immunologist with an emphasis on immune tolerance and autoimmune disease, Dr Gilbert has for the last 25 years focused her research on the immunotoxicity of trichloroethylene (TCE). She has authored over 30 articles examining the immunotoxicity of TCE or related products, and co-edited a book entitled *Trichloroethylene: Toxicity and Health Risks*, Springer, New York/Heidelberg. She is a member of the US EPA's Scientific Advisory Committee on Chemicals (SACC) which has thus far reviewed risk evaluations for ten high-priority chemicals, including TCE, that were identified as part of the Toxic Substances Control Act. Dr. Gilbert has provided risk assessments for human exposure to TCE and other chemicals including perchloroethylene, vinyl chloride, and benzene. Dr. Gilbert is a long-standing member of the Society of Toxicology.

EDUCATION:

Occidental College, Los Angeles, CA, BS, Biology, 1976
Tulane University, New Orleans, LA, PhD, Immunology, 1980

PROFESSIONAL EXPERIENCE:

Postdoctoral Research Associate: Sloan Kettering Institute, New York, NY
1980 -1982
Research Associate, Sloan-Kettering Institute, New York, NY
1982 -1985
Visiting Worker: National Institute for Medical Research, London, UK
1985 -1987
Senior Research Associate: Department of Immunology, The Scripps Research Institute, La Jolla, CA,1987 -1991
Assistant Member (Assistant Professor): The Scripps Research Institute, La Jolla, CA
1991 -1994
Assistant Professor: Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
1995 – 2001
Associate Professor: Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
2001 – 2010
Professor (tenured), Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR
2010- 2017 (Retired)

Secondary Appointments at UAMS: Dept. of Pediatrics, 2002-2017

Dept. of Pharm. and Toxicology, 2010-2017

Adjunct Professor, Dept. of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO, 2017-Present

TEACHING/MENTORING

Teaching Medical Students at UAMS

Course	Total Hours	Level	Years
Medical Microbiology-Immunology-Parasitology Now called *Disease and Defense*	Three-five 1-hour lectures/year Three 3-hour Patient-Oriented Problem Solving sessions/year	2nd year 1st year	1995 – 2011 2011- present

Teaching Graduate Students at UAMS

Course	Total Hours	Level	Years
Immunology	six 1.5-hour lectures/year	1st year	Course Director, 1995 - 2002 Lecturer, 1995 - 2017
Advanced Immunology	three 2-hour lectures/year	2nd-3rd year	1995 -1997
Molecular Mechanisms of Immunology	four 2-hour lectures/year	2nd-3rd year	1998 - 2017
Current Topics in Immunology	two 1-hour lectures/year	1st-5th year	1995 - 2017
Biochemical Methods	two 1.5-hour lectures/year	1st-2nd year	2000 - 2002
Methods in Pharmaceutical Sciences	one 1.5-hour lecture/year	1st-2nd year	2001
Molecular & Translational Toxicology	three 1.5-hour lectures/year	2nd -3rd year	2002 - 2017
Systems Toxicology	three 1.5-hour lectures/year	2nd and 3rd year	2009 - 2017

MENTORING

Dr Gilbert has served as a dissertation/thesis committee chair or member for 22 graduate students at UAMS. She has served as mentoring committee chair or member for 8 junior faculty members at UAMS, and has mentored 21 other undergraduates, graduate students and faculty members as part of INBRE grants or Honors in Research Programs.

RESEARCH/SCHOLARLY WORK

Most Recent Research Support

Title	Funding Agency	Dates	Direct Costs	Role	Effort
Extramural					
Developmental Programming of TCE-induced autoimmune disease R01ES021484	NIEHS	12/1/12 – 11/30/17	$1,372,000	Co-Principal Investigator	30%
Gender Supplement to R01ES021484	NIEHS	9/15/14-10/31/16	$99,724	Co-Principal Investigator	0%
Determining how trichloroethylene alters $CD4^+$ T cell function: 1R01ES017286	NIEHS	1/07/10 - 12/31/14	$675,000	Principal Investigator	40%
Trichloroethylene toxicity and remediation	Competitive grant funded by Organic Compounds Property Contamination class action settlement (CV 1992-002603)	7/01/08-6/30/15	$735,000	Principal Investigator	25%
Training program in the pathophysiology of renal disease: 5T32DK061921 (PI: Portilla)	NIDDK	2006-2011	$603,335	Faculty Mentor	0%
Intramural					
Developing an Immunotoxicology Center in Arkansas	Arkansas Biosciences Institute	7/01/02 – 6/30/17	$1,500,000	Principal Investigator	10%

Past Research Support

Title	Funding Agency	Dates	Direct Costs	Role	Effort
Extramural					

Screening disinfection by-products for their ability to promote autoimmunity	Environmental Protection Agency	10/01/01 -9/31/04	$500,000	Principal Investigator	25%
Mechanisms of chlorinated ethylene-induced autoimmunity, Proposal No. R826409	Environmental Protection Agency	3/25/98 - 3/24/01	$278,356	Principal Investigator	25%
Cyclin-dependent kinase inhibitors mediate T cell anergy: MCB-9817191	National Science Foundation	3/15/99 - 3/14/02	$230,660	Principal Investigator	25%
The use of G1 blockers in a novel system of immune intervention	National Arthritis Foundation	1/1/02 – 12/21/04	$270,000	Principal Investigator	25%
Use of tributyrin as a novel system of immune intervention, Proposal No. KG071598	Arthritis Foundation, Arkansas Chapter	7/15/98 - 10/15/99	$31,280	Principal Investigator	25%
Mechanism of Toxicant-induced T cell Suppression; Grant No. 187-B	American Cancer Society	2/1/96 - 1/31/97	$15,000	Co-principal investigator	25%
A Novel System of Immune Intervention: Grant No. J246	R.W. Johnson Pharmaceutical Research Institute	10/1/92 - 9/30/94	$129,032	Principal Investigator	35%
Mechanisms of renal tubular epithelial cell injury (PI: S. Shah), PO1-DK-58324	NIDDK	2001-2006		Core Director	5%
Suppressor B cells	Arthritis and Rheumatism Council, UK, Project Grant	1986-1987	$45,000	Principal Investigator	100%
Effect of Th cell Tolerance on Cell Cycle Components: Proposal No. MCB-9308198	National Science Foundation	6/1/93 - 5/31/95	$18,000	Principal Investigator	25%
A Novel System of Immune Intervention: Proposal No. 96-B-37	Arkansas Science and Technology Authority Award	1/31/96 - 1/30/97	$33,050	Principal Investigator	30%
Mechanism of B cell suppression	International Union Against Cancer	1985-1986	$16,000	Principal Investigator	100%
National Research Service Award	USPHS	1980-1983		Postdoctoral Fellow	100%
Comparison of the effects of methyl palmitate and glucan on tumor growth	Cancer Association of Greater New Orleans	1978	$900	Graduate Student	100%

Intramural					
Interventive Therapy for Type I Diabetes	Children's University Medical Group	7/1/05-6/31/07	$39,500	Principal Investigator	10%
Inactivating autoreactive T cells by HDAC inhibitors	Sturgis Charitable Trust	2/01/10 – 9/30/10	$24,970	Principal Investigator	0%

Manuscript review activities

Journal	Year Started
Journal of Immunology	1994
Cellular Immunology	1994
Blood	2000
Toxicology and Applied Pharmacology	2006
American Journal of Transplantation	2007
Biochemical Pharmacology	2007
Endocrine	2009
International Journal of Environmental Sciences	2008
Libertas Academica	2009
Toxicological Sciences	2009
Journal of Environmental Science and Health	2010
International Journal of Nephrology and Renovascular Disease	2010
Transplant Immunology	2008
Toxicology	2011
BMC Pharmacology	2011
ISRN Immunology – Editorial Board	2011
Chemical Research in Toxicology	2012
Toxicology Research	2012
Journal of Immunotoxicology – Ad hoc Editor	2012
Environmental and Molecular Mutagenesis	2013
International Journal of Molecular Sciences – Guest Editor for special issue on "Environmental Toxicants and Autoimmune Disease	2013
Drug Design, Development and Therapy	2015
BMC Medical Genomics	2015
Expert Review of Gastroenterology & Hepatology	2015
Environmental Health Insights	2015
Neurotoxicology	2015
Annals of Neurology	2016
PLOS ONE	2016
Inhalation Toxicology	2016

Grant review activities

Agency	Study Section	Years

National Science Foundation	Signal Transduction and Regulation	1996
National Science Foundation	Biocomplexity	2000
Environmental Protection Agency	Experimental Toxicology	2007
National Institutes of Health	Superfund Basic Research (ZES1 LWJ-M)	2009-2015
National Institutes of Health	Systemic Injury by Environmental Exposure (SIEE)	2016
National Institutes of Health	Digestive, Kidney and Urological Systems (DKUS-A)	2009
National Institutes of Health	Immunology (IMM-E)	2009
National Institutes of Health	Infectious Disease and Microbiology (IDM-C) IFG	2009
Wellcome Trust		2006
RJ Reynolds Foundation	External Research Program	2006 2009
Louisiana Board of Regents		2007
UAMS Medical Research Endowment Grant awards Hornick Grant UAMS Pilot Study Grants UAMS Center for Clinical and Translational Research UAMS Bridging Grants ACHRI Children's University Medical Group awards		1999-2017
National Institutes of Health	Environmental Health Sciences Review Committee for T32 applications	2013

PUBLICATIONS (Peer-reviewed):

- Byrum, S.D., Washam, C.L., Patterson, J.D., Vyas, K.K., **Gilbert, K.M**., and Blossom, S.J. Continuous Developmental and Early Life Trichloroethylene Exposure Promoted DNA Methylation Alterations in Polycomb Protein Binding Sites in Effector/Memory CD4$^+$ T Cells**.** *Frontiers in Immunology* Aug 28;10:2016, 2019.
- Khare, S., Gokulan, K., Williams, K., Bai, S., **Gilbert, K.M.**, and Blossom, S.J., Irreversible effects of trichloroethylene on the gut microbial community and gut-associated immune responses in autoimmune-prone mice, *Journal of Applied Toxicol*ogy 39:209 2019.
- Blossom, S.J**.** and **Gilbert, K.M**. Epigenetic underpinnings of developmental immunotoxicity and autoimmune disease. *Current Opinion in Toxicology* 10:23-30, 201, 2018

- Blossom, S.J., Fernandes, L., Bai, S., Chare, S., Gokulan, K., Yuan, Y., Dewall, M., Simmen, F.A., and **Gilbert, K.M**., Opposing actions of developmental toxicity and high-fat diet coexposure on markers of lipogenesis and inflammation in autoimmune-prone mice, *Toxicological Science*, 164:313-327, 2018.
- **Gilbert, K.M**., Blossom, S.J., Reisfeld, B., Erickson, S.W., Vyas, K., Maher, M. Broadfoot, B., West, K., Bai, S., Cooney, C.A., and Bhattacharyya, S., Trichloroethylene-induced alterations in DNA methylation were enriched in polycomb protein binding sites in effector/memory CD4+ T cells, *Environmental Epigenetics* 3. Epub 2017.
- Frye, R.E., Rose, S., Wynne, R., Bennuri, S.C., Blossom, S., **Gilbert, K.M**., Heilbrun, L., and Palmer, R.F., Oxidative stress challenge uncovers trichloracetaldehyde hydrate-induced mitoplasticity in autistic and control lymphoblastoid cell lines, *Science Report* 7:4478, 2017.
- **Gilbert, K.M**., Bai, S., Barnette, D., and Blossom, S.J. Exposure cessation during adulthood did not prevent immunotoxicity caused by developmental exposure to low-level trichloroethylene in drinking water. *Toxicological Science* 157: 429-437, 2017
- Meadows, J.R., Parker, C., **Gilbert, K.M**., Blossom, S.J., and Dewitt, J.C., A single dose of trichloroethylene given during development does not substantially alter markers of neuroinflammation in brains of adult mice. *Immunotoxicology* 14:95-102, 2017.
- **Gilbert, K.M.**, Blossom, S.J., Erickson, S.W., Broadfoot, B., West, K., Bai, S. and Cooney, C.A. Chronic exposure to trichloroethylene increases DNA methylation of the ifng promoter in $CD4^+$ T cells. *Toxicology Letters*, 260:1-7, 2016.
- **Gilbert, K.M.**, Blossom, S.J., Erickson, S.W., Reisfeld, B., Zurlinden T.J., Broadfoot, B., West, K., Bai, S. and Cooney, C.A. Chronic exposure to water pollutant trichloroethylene increased epigenetic drift in $CD4^+$ T cells. *Epigenomics*, 8:633-649, 2016.
- **Gilbert, K.M.**, Reisfeld, B., Zurlinden T.J., Kreps, M.N., Erickson, S.W. and Blossom, S.J. Modeling toxicodynamic effects of trichloroethylene on liver in mouse model of autoimmune hepatitis. *Toxicology and Applied Pharmacology*, 279:284-293, 2014.
- **Gilbert, K.M**., Woodruff, W. and Blossom, S.J., Differential Immunotoxicity induced by two different windows of developmental trichloroethylene exposure, *Autoimmune Diseases.* Epub 2014
- **Gilbert, K.M**. Autoimmunity Hepatitis. *Encyclopedic Reference of Immunotoxicology,* Vohr, Hans-Wener (Ed), Springer Publishing Co., 2013.
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- Fontenelle, B. and **Gilbert, K.M.,** n-Butyrate anergized effector CD4+ T cells independent of regulatory T cell generation or activity, *Scandinavian Journal of Immunology*, 76:457-463, 2012.
- **Gilbert, K.M.**, Nelson, A.R, Cooney, C.A., Reisfeld, B., and Blossom, S.J. Epigenetic alterations may regulate temporary reversal of $CD4^+$ T cell activation

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- Dagtas, A.S., Edens, R.E. and **Gilbert, K.M.** Histone deacetylase inhibitor uses $p21^{Cip1}$ to maintain anergy in $CD4^+$ T cells. *International Immunopharmacology*, 9:1289-1297, 2009.
- **Gilbert, K.M.,** Przybyla, B., Pumford, N.R., Han, T, Fuscoe, J., Schnackenberg, L.K., Holland, R.D., Doss, J.C. MacMillan-Crow, L, and Blossom, S.J. Delineating liver events in trichloroethylene-induced autoimmune hepatitis, *Chemical Research in Toxicology* 22: 623-632, 2009.
- **Gilbert, K.M.,** Blossom, S.J., and Pumford, N. Comments on "Lifetime exposure to trichloroethylene (TCE) does not accelerate autoimmune disease in MRL+/+ mice, *Journal of Environmental Health Sciences*, Part A, 44:116, 2009.
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- **Gilbert, K.M.** and Luebke, R. Overview of Platform Session "Immunotoxicology": Society of Toxicology 45th Annual Meeting, *Journal of Immunotoxicology,* 3: 213-216, 2006.
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- Blossom, S.J. and **Gilbert, K.M**. Ability of environmental toxicant trichloroethylene to promote immune pathology is strain-specific. *Journal of Immunotoxicology* 3:179-188, 2006.
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- **Gilbert, K.M**., Boger, S. and Fifer, E.K.. Butyric acid derivative induces allospecific T cell anergy and prevents graft-versus-host disease. *Immunopharmacology and Immunotoxicology* 25:13-27, 2003.
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Book Chapters:

- **Gilbert, K.M**. *Trichloroethylene and Autoimmunity in Human and Animal Models* in Trichloroethylene: Toxicity and Health Risks, Edited by **Gilbert, K.M** and Blossom, S.J. Springer. 15-36, 2014.
- Wartenberg, D. and **Gilbert, K.M**. *Trichloroethylene and Cancer* in Trichloroethylene: Toxicity and Health Risks, Edited by **Gilbert, K.M** and Blossom, S.J. Springer. 171-185, 2014.
- Cooney, C.A., and **Gilbert, K.M**. *Toxicology, Epigenetics and Autoimmunity* in Toxicology and Epigenetics, Edited by Saura C. Sahu. Wiley-Blackwell Inc. 241-252, 2012.
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Platform presentations

- **Gilbert, K.M.** Autoimmune-prone versus normal mice as models for toxicant-mediated autoimmune disease. In Workshop: Strengths and weaknesses of mice as a model for humans in studies of immunological effects of drugs and chemicals , Society of Toxicology, San Diego, March, 2015.
- **Gilbert, K.M**. Trichloroethylene exposure and epigenetic alterations in T cell function. In Prenatal Programming and Toxicity IV, Boston, MA, October, 2014
- **Gilbert, K.M**. Autoimmune disease triggered by trichloroethylene is associated with epigenetic alterations in $CD4^+$ T cells." In Environmental Health 2013, Science and Policy to Protect Future Generations, Boston, MA, March, 2013
- **Gilbert, K.M**. Chronic exposure to water pollutant trichloroethylene promotes autoimmune hepatitis and induces epigenetic alterations in $CD4^+$ T cells. In Symposium entitled "Role of Environmental Exposures in the Development of Autoimmune Disease", The American Association of Immunologists Annual Meeting, Boston, MA, 2012.
- **Gilbert, K.M**. Environmental pollutants that trigger immune dysfunction and promote autoimmune disease. Keynote speaker at FDA's National Center for Toxicological Research Office of Women's Health Research Update Program, August 10, 2012.
- **Gilbert, K.M**. Trichloroethylene-induced autoimmunity; dependence on metabolism and genetic susceptibility, In Workshop entitled "Autoimmunity

versus systemic hypersensitivity: commonalities useful for toxicity testing", Society of Toxicology Annual Meeting, 2011.

- **Gilbert, K.M**., Rowley, B., Hennings, L., and Blossom, S.J. Co-exposure to mercury accelerates autoimmunity induced by trichloroethylene, NCTR Women's Health Research Workshop, Little Rock, September, 2010.
- **Gilbert, K.M**., Rowley, B., Hennings, L., and Blossom, S.J. Mice exposed to a binary mixture of immunotoxicants developed unique autoimmune effects not induced by single exposure, 49th Society of Toxicology Annual Meeting, Salt Lake City, Utah, March, 2010.
- **Gilbert, K.M.,** Przybyla, B., Pumford, N.R., Han, T, Fuscoe, J., Schnackenberg, L.K., Holland, R.D., Doss, J.C. MacMillan-Crow, L, and Blossom, S.J. Combining transcriptomics and metabolomics to delineate immunotoxicity of trichloroethylene, NSF Advance Program Planning meeting, Petit Jean, AR, March, 2009.
- **Gilbert, K.M.,** Yeung, S., Nelson, A., and Przybyla, B., Susceptibility factors in trichloroethylene-induced autoimmunity, South Central Society of Toxicology annual meeting, NCTR, Jefferson, AR, September, 2008.
- **Gilbert, K.M**., Whitlow, A.B., and Pumford, N.R., Environmental toxicant associated with the development of autoimmune disease stimulates T cell signaling, Environmental Factors in Autoimmune Disease, NIEHS, Durham, NC, February, 2003.
- **Gilbert, K.M**., Whitlow, A.B. and Pumford, N.R. Environmental contaminant associated with induction of autoimmune disease stimulates T cells via Schiff base formation, American Association of Immunologists Annual Meeting, New Orleans, LA, April, 2002.
- **Gilbert, K.M**., Fecher, N.B., Freeman, J.P., Wahid, R. and Fifer, E.K. Potential clinical use of butyric acid prodrugs to induce antigen-specific T cell inactivation. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- **Gilbert, K.M**., M.L. Thoman, K. Bauche, and Weigle, W.O., TGF-β1-induced tolerance in antigen-specific naïve T cells, The 9th International Congress of Immunology, San Francisco, July, 1995.
- **Gilbert, K.M.** and Weigle, W.O. Use of G1a blockers to induce antigen-specific T cell anergy, New Strategies for Selective Immune Suppression, Cambridge Healthtech Institute, Waltham, MA, October, 1994.
- **Gilbert, K.M.,** and Weigle, W.O., Activated B cells which express CTLA-4 counter-receptors are tolerogenic. American Association of Immunologists Annual Meeting, Anaheim, April, 1994.
- **Gilbert**, **K.M.** and Weigle, W.O., Activation does not reverse B cell tolerogenicity, American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.
- **Gilbert, K.M.,** Hobbs, M.V. Ernst, D.N., and Weigle, W.O., Heterogeneity in the ability of different antigen presenting cells to tolerize Th1 and Th2 clones, American Association of Immunologists Annual Meeting, 1992.
- **Gilbert, K.M.** Effects of tolerance induction on cell cycle progression by the Th1 and Th2 clones, 18th Annual Conference of the La Jolla Immunologists, San Diego, CA, 1991.

- **Gilbert, K.M**. Hoang, K.D. and Weigle, W.O., Tolerized high density Th clones lose bystander helper activity, American Association of Immunologists Annual Meeting, April, 1989.
- **Gilbert, K.M.** and Weigle, W.O. B cell activation by T helper cells. MidWinter Conference of Immunologists, Asilomar, CA., 1988.
- **Gilbert**, **K.M.** and Hoffmann, M.K. cAMP as a 2nd messenger in antibody production by B cells. American Association of Immunologists Annual Meeting, Anaheim, April, 1985.

- **Sessions Chaired:**

- "Epigenetics" as Presented at the 51st Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Platform Session "Developmental Immunotoxicology, Host Resistance and Genomics, Society of Toxicology Meeting, Seattle, 2008.
- Platform Session "Immunotoxicity" Society of Toxicology Annual Meeting, San Diego, CA, 2006.
- Co-chaired Symposia "T cell inactivation and apoptosis", American Association of Immunologists Annual Meeting, San Francisco, April, 1998.
- Co-chaired Immunology session for American Society of Microbiology, South Central Branch, Little Rock, AR, 1995
- Co-chaired Symposium "T cell tolerance and anergy", American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1994.
- Co-chaired Symposium "T cell regulation," American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.

- **Other Invited Presentations:**

- "Environmental pollutants as triggers of autoimmune disease" Distinguished Speaker, Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, April 22, 2015.
- "Trichloroethylene as a trigger of autoimmune disease." In Society for Women's Health Research Autoimmune Disease Roundtable, Washington, D.C., October 5, 2012.
- Trichloroethylene-induced autoimmunity; dependence on metabolism and genetic susceptibility, In Workshop entitled "Autoimmunity versus systemic hypersensitivity: commonalities useful for toxicity testing, Society of Toxicology Annual Meeting, 2011.
- Developing an immunotoxicology center in Arkansas, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR, September, 2010.
- Co-exposure to mercury accelerates autoimmunity induced by trichloroethylene, International Congress of Toxicology, Barcelona, Spain, July, 2010.

- Developing an immunotoxicity center in Arkansas, Arkansas Children's Hospital Research Institute Board, May, 2010.
- Environmental pollutants as triggers for autoimmune disease, South Central Branch ASM, Nicholls State University in Thibodaux, LA, November 2009.
- Contribution of environmental pollutants to autoimmune disease, Jones Eye Center Seminar Series, Little Rock, AR, June 2008.
- Combining transcriptomics and metabolomics to delineate immunotoxicity of trichloroethylene, Society of Toxicology Annual Meeting, Seattle, WA, March, 2008.
- Histone deacetylase inhibitors block MAP kinases to induce tolerance in Th1 cells, The University of Pennsylvania School of Medicine, Department of Pathology and Laboratory Medicine, Division of Transplantation Immunology Seminar Series, Philadelphia, PA, May 16, 2007
- Examining the genetic susceptibility to the immunotoxicity of a trichloroethylene metabolite, Society of Toxicology Annual Meeting, Charlotte, NC, March, 2007.
- Distinguished Speaker: Environmental contaminant and Superfund chemical trichloroethylene promotes autoimmune disease and inhibits T cell apoptosis", Bench to Bedside Symposium: Immunomodulation by Environmental Factors: The role of the Environment in Autoimmune Disease, Center for Immunopathology and Microbial Pathogenesis, Morgantown, West Virginia, December, 2006.
- Environmental contaminant trichloroethylene promotes autoimmune disease and inhibits T cell apoptosis, Society of Toxicology Annual Meeting, San Diego, CA, March, 2006.
- Contribution of environmental contaminants to autoimmune disease, Workshop on Lupus and the Environment: Disease Development, Progression and Flares, NIEHS, Washington, DC, September, 2005.
- The environmental toxicant trichloracetaldehyde promotes activation and inhibits apoptosis of mature T lymphocytes by inhibiting fas ligand expression, 12th International Congress of Immunology, Montreal, Canada, 2004.
- Butyric acid derivative induces allospecific T cell tolerance, Arthritis Foundation Research Conference, Keystone Resort, Colorado, June, 2003
- Why you should go with the flow; new research applications for flow cytometry, Okie-Arkie Bi-State Meeting, Little Rock, Arkansas, April, 2003
- Novel G1 blocker inhibits antigen-specific T cell response and prevents graft-versus-host disease, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR 2002
- Autoimmunity, Research Council, College of Medicine, UAMS. Research Retreat I, Advancing collaborative research and funding strategies, Little Rock, AR, 2001
- Why you should go with the flow, Pharmaceutical Sciences Seminar, UAMS, 2001
- T cell anergy linked to alterations in cell cycle regulatory proteins. American Association of Immunologists Annual Meeting, San Francisco, April, 1998.
- G1 blockers induce anergy in CD4^{+}T cells, American Association of Immunologists Annual Meeting, New Orleans, LA., June, 1996.

- T cell tolerance as immunotherapy, Hematology Oncology Research Seminar Series, Arkansas Cancer Research Center, November, 1995
- Activated B cells which express CTLA-4 counter-receptors are tolerogenic, American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1994.
- Use of G1 blockers to induce Th cell anergy, Glaxo Institute for Molecular Biology, Geneva, Switzerland, January, 1994.
- T cell tolerance, American Association of Immunologists Annual Meeting, Anaheim, CA, April, 1992.
- Effects of tolerance induction on cell cycle progression by the Th1 and Th2 clones, Annual Conference of La Jolla Immunologists, La, Jolla, CA, November, 1991.

Other abstracts/posters presentations:

- Zurlinden, TJ, **Gilbert, KM**, and Reisfeld,B. A computational approach for characterizing subtle changes in DNA methylation in $CD4^+$ T cells. FutureTox III, Arlington, VA, November, 2015.
- **Gilbert, KM**, Cooney, C , Broadfoot, B., Chandler, G. and Blossom, SJ. Long-term exposure to water pollutant trichloroethylene increased plasticity of DNA methylation in *Ifng* promoter and induced non-monotonic *Ifng* expression in effector/memory $CD4^+$ T cells, Gordon Conference Cellular & Molecular Mechanisms of Toxicity, Andover, NH, 2015.
- **Gilbert, KM**, Cooney, C., and Blossom, S. Autoimmune disease triggered by trichloroethylene is associated with epigenetic alterations in $CD4^+$ T cells, 52^{nd} Annual Society of Toxicology meeting, San Antonio, Texas, March, 2013.
- **Gilbert, KM**, Nelson, A., Cooney, C., and Blossom, S. Subchronic trichloroethylene exposure alters epigenetic processes in $CD4^+$ T cells, 51^{st} Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Blossom, SJ, Melnyk, **Gilbert, KM,** and James, J. Postnatal trichloroethylene modulates redox status and oxidative stress in mouse hippocampus, 51^{st} Annual Society of Toxicology meeting, San Francisco, CA, March, 2012.
- Blossom, SJ, Melnyk, S, **Gilbert, KM**, James SJ. Differential Expression of Neuroimmune Mediators Following Postnatal Exposure to Trichloroethylene. The 27^{th} International Neurotoxicology Conference; Environmentally Triggered Neurodevelopmental Disorders: Focus on Endocrine Disruption and Sex Differences in Autism, ADHD, and Schizophrenia, Research Triangle Park, NC**.** October 30-November 2, 2011.
- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Altered Redox Status and Oxidative Stress in Hippocampus of Mice Postnatally Exposed to Trichloroethylene, Arkansas Biosciences Institute Fall Research Symposium, September 21, 2011.
- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Maternal and early life trichloroethylene exposure modulates gene expression of chemokines and

neurotrophins in the brain, 50th Annual Society of Toxicology meeting, Washington DC. March 10, 2011.

- Blossom SJ, Melnyk S, **Gilbert KM**, James SJ. Neuroimmune dysregulation with developmental exposure to trichloroethylene in a mouse model relevant to neurodevelopmental disorders, Arkansas Biosciences Institute Fall Research Symposium, Little Rock, AR. September 29. 2010.
- **Gilbert, K.M.,** Boger,S., Fifer, and Price, P. T cell tolerance induced by novel G1 blocker is mediated by cyclin-dependent kinase inhibitor p21cip1, 12th International Congress of Immunology, Montreal, Canada, 2004.
- Blossom, S.J., and **Gilbert, K.M**. Trichloroethylene-induced autoimmunity, Environmental Factors in Autoimmune Disease, NIEHS, Durham, NC, February, 2003.
- **Gilbert, K.M**., DeLoose, A., and Jackson, S.K. n-Butyrate-induced Th1 cell anergy associated with $p21^{Cip1}$ inhibition of MAPK pathway. American Association of Immunologists Annual Meeting, New Orleans, LA, April, 2002.
- **Gilbert, K.M**., Jackson, S.K., and DeLoose, A. Th1 cell anergy is associated with increased levels of both $p21^{Cip1}$ and $p27^{Kip1}$. American Association of Immunologists Annual Meeting, Orlando, FL, April, 2001.
- Brand, K.A., **Gilbert, K.M**., Yingyun, C., E. Kim Fifer, E.K., Synthesis of butyric acid derivatives as immune response modulators. Western Region Merck Pharmacy Research Seminar, Denver, CO, June, 2001.
- Jackson, S.K. and **Gilbert, K.M**. Anergy induction in Th1 cells increases expression of cyclin-dependent kinase inhibitors. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- **Gilbert, K.M**. and Blossom, S.J. B cells from autoimmune BXSB mice are hypo-responsive to signals provided by CD4+ T cells. American Association of Immunologists Annual Meeting, Seattle, May, 2000.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Trichloroethylene accelerates an autoimmune response in MRL+/+ mice at doses similar to human exposure levels. Society of Toxicology, New Orleans, La, March, 1999.
- Fecher, N.I.P., **Gilbert, K.M.** Wahid, R. and Fifer, E.K., Butyric acid prodrugs as modulators of immune response. Western Region Merck Undergraduate Pharmacy Research Seminar", University of Colorado School of Pharmacy, Denver, CO, June, 1999.
- Blossom, S. Chu, E.B., Weigle, W.O. and **Gilbert, K.M**. B cells from autoimmune BXSB mice express CD40 ligand. American Association of Immunologists Annual Meeting, San Francisco, April, 1998
- Griffin, J.M., **Gilbert, K.M.,** and Pumford, N.R. Cytochrome P450 2E1 activation of trichloroethylene initiates a Th_1 T cell response in MRL+/+ mice. Linking Environmental Agents and Autoimmune Diseases, National Institutes of Environmental Health and Safety, 1998.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Acceleration of an autoimmune response in MRL+/+ mice exposed to trichloroethylene at doses similar to human exposure levels. South Central Society of Toxicology, 1998.
- Griffin, J.M**.,** Wong, J., Blossom, S.M., Jackson, S.K., **Gilbert, K.M**., and Pumford, N.R., Immunomodulation induced by trichloroethylene-in the

autoimmune prone MRL+/+ mice. Society of Toxicology, Seattle, WA, March, 1998.

- Blossom, S. and **Gilbert, K.M.** B cells from autoimmune BXSB mice express CD40 ligand. UAMS Student Research Day, Won second prize for best graduate student presentation, April, 1997.
- Blossom, S., Chu, E.B., Weigle, W.O., and **Gilbert, K.M**. , Role of CD40L+ B cells in autoimmune BXSB mice, SLE Foundation annual meeting, National Institute of Health, November, 1997.
- Griffin, J.M., **Gilbert, K.M**., and Pumford, N.R. Trichloroethylene-induced autoimmunity in MRL/++ mice, South Central Chapter of the Society of Toxicology, Jefferson, AR, November, 1997.
- Blossom, S., **K.M. Gilbert**, Increased expression of costimulator molecules on antigen presenting cells in the BXSB mouse model of systemic lupus erythematosus, American Association of Immunologists Annual Meeting, New Orleans, LA, June, 1996.
- Blossom, S. and **Gilbert, K.M**. Irregular expression of costimulator molecules on antigen presenting cells in the BXSB mouse model of systemic lupus erythematosus, American Society of Microbiology, South Central Branch, Little Rock, AR, November, 1995.
- Weigle, and **Gilbert, K.M**., Th1 cell anergy and G1a blockade. American Association of Immunologists Annual Meeting, May, Denver, CO, 1993.
- **Gilbert**, **K.M.,** Ernst, D.N., Hobbs, M.V., and Weigle, W.O. Cell cycle progression by tolerized Th1 and Th2 clones. American Association of Immunologists Annual Meeting, Anaheim, April, 1992.
- Rothermel, A.L., Ernst, D.N., Hobbs, M.V., Weigle, W.O., and **Gilbert, K.M.** Ability of tolerized Th1 and Th2 clones to stimulate B cell activation and cell cycle progression. American Association of Immunologists Annual Meeting, Anaheim, April, 1992.
- Rothermel, A.L., **Gilbert, K.M.** and Weigle, W.O., Induction of polyclonal B cell proliferation by activated T helper cells and their lymphokines, American Association of Immunologists Annual Meeting, April, 1989.

LEADERSHIP

Examples of Leadership Roles at UAMS

Role	Responsibility	Affiliation	Years
Director	Arkansas Center for Environmental Exposure Research: ACEER was initiated in 2002, and since then received over 3 million dollars in extramural grant support from the NIH and other sources, and 1.6 million dollars in intramural support from the Arkansas Biosciences Institute. It provided salary and/or infrastructure support to recruit and/or retain 10 faculty members and 20 undergraduate and graduate students in 5 institutions around the state, thus enabling them to work together on common issues concerning environmental contamination and remediation.	UAMS/ACHRI	2002 - 2017
President	Women's Faculty Development Caucus (WFDC)	UAMS	2005 - 2007
Co-Director and then on organizing committee	**UAMS Graduate School Career Day**. Current graduate students, and undergraduates from all over Arkansas and surrounding states visit UAMS to hear about our graduate program, and to learn about career opportunities for PhDs.	UAMS	2002 - 2017

PROFESSIONAL RECOGNITION/ADVOCACY FOR WORK WITH TCE

- 2005: Participated in National Institutes of Health Workshop on Lupus & the Environment; Disease Development, Progression and Flares. I represented the work done on solvents and autoimmune disease at this workshop organized by the NIH to develop grant funding on the subject of environmental pollutants and the development of lupus.
- 2006: Consulted with the Committee on Human Health Risks of Trichloroethylene, National Research Council during the development of document entitled *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*,
- 2007: Consulted with Pew Charitable Trust Environmental Working Group for "Kid-Safe Chemicals Act of 2008" bill before US Congress.

- 2008: Featured in *The Autoimmune Epidemic* by Donna Jackson Nakazawa, Simon & Schuster, New York
- 2008: Featured in "The Scariest Health Threat You've Never Heard Of" in *Glamour*, September
- 2009: Participated in the EPA Science Advisory Board's review of the Trichloroethylene (TCE) health assessment
- 2013: Served on an expert panel that reviewed EPA TSCA Workplan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses
- 2014: Served on a TCE Information Group tasked with assisting the NTP Office of the Report on Carcinogens as they considered a possible change in listing status for TCE in the Report on Carcinogens. Specifically, we were asked to provide comments on whether the information concerning the immunotoxicity of TCE provided biological plausibility for TCE-related cancers.
- 2014: Worked with the Arkansas Department of Environmental Quality and the Arkansas Department Health to identify TCE-contaminated sites in Northern Arkansas, and to identify toxicant-induced autoimmune disease in people living near the sites
- 2017: Selected as a permanent member of the Scientific Advisory Committee on Chemicals (SACC) (Toxic Substances Control Act), for the US Environmental Protection Agency. The SACC is tasked with providing independent advice and expert consultation on issues related to the implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act which amends the Toxic Substances Control Act. The first 10 chemicals reviewed included trichloroethylene, tetrachloroethylene (perchloroethylene), carbon tetrachloride, methylene chloride, 1-bromopropane, n-methyl pyrrolidone, 1,4-dioxane, pigment violet 29, asbestos, and cyclic aliphatic bromide cluster.
- 2019: As requested by the National Academy of Sciences reviewed a report prepared by the National Academies Board on Environmental Studies and Toxicology concerning their review of the *DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*

LITIGATION HISTORY

Case	Law Firm	Contribution	Outcome
Jodelle L. Kirk v Schaeffler Group USA Inc.: FAG Bearings, LLC, 2016 United States District Court Western District of Missouri, Cause No 3:13-cv-0503	Humphrey, Farrington, & McClain	Wrote expert report on TCE Deposed Testified at trial as to general and specific causation	Plaintiff awarded $20.6 million dollars
Hostetler, et al. vs Johnson Co, Inc, et al. 2018 United Stated District Court Northern District of Indiana Cause No. 3:15-CV-226JD-MGG	Taft Stettinius & Hollister LLP	Wrote expert report on TCE general causation increasing risk for autoimmune diseases and cancer Deposed	Settled in 2023
Asher, et al. v Raytheon Technologies Co, et al. Huntington Superior Court State of Indiana Cause No. 35D-01-2006-CT-000338 Emergency hearing to determine health risks of the drinking water in Andrews, Indiana, 2020	Taft Stettinius & Hollister LLP	Wrote Affidavit concerning human health effects of vinyl chloride and cis-1,2-Dichloroethylene in water supply Testified at remote hearing Deposed 4-16-24	Emergency action was denied
Millman, Powell and Powell vs Raytheon Technologies F/k/a United Technologies et al. Corporation, 2021 Northern District of Indiana Cause No.:1:16-cv-00312-HAB-SLC	Taft Stettinius & Hollister LLP	Wrote expert report on human health effects of trichloroethylene, vinyl chloride, benzene, and cis-1,2-Dichloroethylene Performed risk assessments for 3 plaintiffs Opinioned that toxicant exposure contributed to development of liver cancer and trigeminal neuralgia in 2 plaintiffs Deposed	Ongoing

Houlihan vs United Technologies Corporation, 2019 Huntington Superior Court State of Indiana Cause No. 35C01-1803-CT-000144	Taft Stettinius & Hollister LLP	Wrote expert report on the ability of trichloroethylene, vinyl chloride and benzene to promote immunotoxicity and cancer Deposed	Ongoing
Funderburk et al. vs Johnson Controls, Inc. and TOCON Holdings, LLC, 2021	Taft Stettinius & Hollister LLP	Wrote expert report concerning the human health effects of trichloroethylene, perchloroethylene, vinyl chloride and cis-1,2-Dichloroethylene Performed risk assessments for 94 plaintiffs Deposed 8-30-23	Ongoing
Taylor et al. v Schaeffler Group., et al (Case No.:20AO-CC0341)	Humphrey, Farrington & McClain Independence, Missouri	Trichloroethylene general causation Deposed 5-17-23	
Preliminary research, 2022	Mueller Law Offices, Austin Texas	Generated report on epidemiological studies linking trichloroethylene exposure and human health	
Preliminary research, 2022	Romanucci & Blandin, Chicago, IL	Performed risk assessments for 19 plaintiffs	

Appendix B

Fee Schedule

Kathleen M. Gilbert, PhD
Immunotoxicologist

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- Hourly charge for document and record review: $400
- Hourly charge for consulting over the phone: $250
- Hourly charge for affidavit/report writing: $450
- Hourly charge for deposition: $500
- Hourly charge for trial testimony: $500