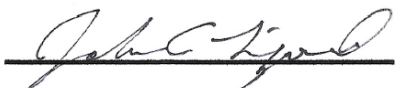


# Exhibit 146

**Expert Report of**  
**John C. Lipscomb, Ph.D., DABT,**  
**Fellow of the Academy of Toxicological Sciences**

**Camp Lejeune Justice Act**  
**United States Federal Court**  
**Eastern District of North Carolina**

Prepared for  
United States Department of Justice  
950 Pennsylvania Avenue NW  
Washington, DC 20530



**John C. Lipscomb, PhD, DABT, FATS**

**February 7, 2025**

**Lipscomb and Associates, PLLC**  
7501 Glenn Hills Drive  
Sherwood, AR 72120  
513.470.0409

# CONTENTS

1.	LIST OF ACRONYMS.....	5
2.	LIST OF OPINIONS .....	7
3.	QUALIFICATIONS .....	9
4.	EXECUTIVE SUMMARY .....	11
5.	BIOLOGY AND TOXICOLOGY .....	15
5.1.	Environmental Concentrations are Not Exposure; Exposures are Not Doses; Doses are Not Tissue Concentrations.....	15
5.2.	Cells and Tissues Respond to Stimuli to Maintain Homeostasis.....	16
5.3.	Biological Response is the Result of a Particular Toxicity Pathway.....	18
5.3.1.	Not all changes are adverse.....	19
6.	WHAT IS RISK ASSESSMENT?.....	20
6.1.	The Likelihood of an Effect or Response is a Function of Exposure or Dose.....	20
6.2.	Risk Values .....	22
6.3.	Exposure Assessment .....	22
7.	RISK ASSESSMENT IS NOT A MEASURE OF TRUE RISK BECAUSE OF THE HEALTH CONSERVATIVE ASSUMPTIONS INVOLVED .....	24
8.	CONSERVATIVENESS OF RISK ASSESSMENT QUANTITATIVE METHODS.....	27
8.1.	What does “Conservatism” Mean? .....	27
8.2.	What is Non-cancer Risk Assessment? .....	28
8.3.	What are Non-Cancer Reference Values?.....	28
8.4.	The PHA’s Use of Reference Values .....	30
8.4.1.	Risk Values Developed for Longer Durations will Over-Estimate Risk .....	32
	from Shorter Exposures .....	32
8.5.	Non-Cancer Risk Values are Developed Through a Multi-Step Process .....	35
8.5.1.	The Method to Derive MRL values and EPA Reference Values Incorporates a Level of Conservatism Which is Then Imported into all Risk Assessments.....	36
8.6.	Identifying the Candidate Critical Effects.....	37
8.7.	The Dose Response Analysis.....	38
8.8.	Determining the POD Value Underestimates the True Threshold for the Response.....	39
8.9.	The Point of Departure Dose is Identified, then Reduced.....	41
8.9.1.	POD Values do not Capture Dose Response Data, and so Prevent the Ability of Risk Values to Quantify Increased Risk.....	42

8.10.	Uncertainty Factors Cover Data Gaps and Reduce the Point of Departure.....	43
8.11.	What is Cancer Risk Assessment?.....	46
8.11.1.	Mode of Action-Based Conservatism in Cancer Risk Assessment .....	47
8.11.2.	Exposure Assumption- Associated Conservatism in Cancer Risk Assessment.....	48
8.11.3.	Point of Departure-Based Conservatism in Cancer Risk Methods.....	48
8.11.4.	Duration-Associated Conservatism in Cancer Risk Assessment.....	49
8.12.	Cancer Risk Potency Factors Cannot Quantify Risk .....	51
8.12.1.	ATSDR’s Cancer Risk Evaluation Guideline (CREG) Values Cannot Quantify Risk .....	51
9.	HAZARD QUOTIENT AND HAZARD INDEX VALUES .....	52
9.1.	Hazard Quotient and Hazard Index Values Address Only Exposure. ....	53
9.2.	How Should HQ Values Be Interpreted?.....	54
9.3.	Chronic Reference Values Over-Estimate the Potential for Health Effects Resulting from Less-Than-Lifetime Exposures.....	56
10.	THE RESULTS OF A RISK ASSESSMENT MUST BE PRESENTED AND INTERPRETED IN THE CONTEXT OF THE PURPOSE FOR WHICH THE ASSESSMENT WAS CONDUCTED.....	58
10.1.	Risk Assessments are Decision-Making Tools, Not Point Estimates .....	58
10.2.	Screening Approaches are Worst-Case Scenarios .....	59
10.3.	EPA Reference Values Cannot Be Used to Quantify Risk .....	59
10.4.	ATSDR’s MRL Values Cannot Be Used to Quantify Risk.....	60
10.5.	ATSDR’s EMEG and RMEG Values Cannot be Used to Quantify Risk .....	61
10.6.	Several Issues Common to Many Non-cancer Risk Values .....	62
10.6.1.	Chronic Reference Values Over-Estimate Short-Duration Risk .....	62
10.6.2.	Uncertainty Factors Substantially Reduce Risk Values.....	63
10.7.	Hazard Quotients and Hazard Index Values Cannot be Used to Quantify Risk .....	63
10.7.1.	Hazard Quotient and Hazard Index Values Address Exposure .....	64
10.7.2.	Acceptable Level Values are Biased to Develop Higher Hazard Quotient Values .....	64
10.7.3.	Dose Response Information is Key to Interpreting Hazard Quotient Values .....	65
10.7.4.	All Hazard Quotient Values Are Not Equal .....	65
10.7.5.	Additional Issues in the PHA’s interpretation of HQ and HI Values .....	66
10.8.	Interpreting the Hazard Quotient and Hazard Index Values in the PHA.....	67
10.9.	Exposure Estimates are Often Worst-Case and Nearly Implausible .....	68
10.10.	Pharmacokinetically-Based Risk Errors for Camp Lejeune Exposures.....	68
10.11.	Properly Bounding Conclusions Reached from Preliminary Analyses is Necessary.....	69
11.	MAXIMUM CONTAMINANT LEVEL VALUES CANNOT BE USED TO QUANTIFY RISK .....	72

12. CHEMICAL MIXTURES AND INTERACTIONS ..... 76  
12.1. Not All Mixtures Cause an Interaction that Increases Toxicity ..... 76  
12.1.1. Metabolism of Chemical Mixtures ..... 77  
12.2. Synergistic Interactions do Not Occur for Camp Lejeune Chemicals..... 78  
13. EPA’s Ban of TCE Does Not Apply to Drinking Water Contamination at Camp Lejeune..... 81  
14. CONCLUSION..... 83  
15. REFERENCES ..... 85  
16. APPENDIX A..... 97

## 1. LIST OF ACRONYMS

c-1,2-DCE	cis-1,2-Dichloroethylene
t-1,2-DCE	trans-1,2-Dichloroethylene
ABT	American Board of Toxicology
AL	Acceptable Level
AOP	Adverse Outcome Pathway
ATS	Academy of Toxicological Sciences
ATSDR	Agency for Toxic Substances and Disease Registry
EPA	U.S. Environmental Protection Agency
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower Confidence Bound
BMR	Benchmark Response
COI	Chemical(s) of Interest
CREG	Cancer Risk Evaluation Guide
CSAF	Chemical-Specific Adjustment Factor
CUF	Combined Uncertainty Factor
CV	Comparison Value
DABT	Diplomate, American Board of Toxicology
DDEF	Data Derived Extrapolation Factor
DNA	Deoxyribonucleic Acid
DR	Dose Response
E	Exposure
EA	Exposure Assessment
EMEG	Environmental Media Evaluation Guide
HI	Hazard Index
HID	Hazard Identification
HQ	Hazard Quotient
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
LADD	Lifetime Average Daily Dose
LOEAL	Lowest Observed Adverse Effect Level
MCB	Marine Corps Base
MCL	Maximum Contaminant Level
MCL-G	Maximum Contaminant Level - Goal
MRL	Minimal Risk Level
mg	Milligram
mg/kg/d	Milligram per kilogram body weight per day
mg/kg-d	Milligram per kilogram body weight per day
mg/L	Milligram per liter
mg/m <sup>3</sup>	Milligram per cubic meter
MOA	Mode of Action
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
OSCPP	Office of Chemical Safety and Pollution Prevention

OSF	Oral Slope Factor
OW	Office of Water
PBPK	Physiologically Based Pharmacokinetic
PCE	Tetrachloroethylene
PHA	Public Health Assessment
PHAGM	Public Health Assessment Guidance Manual
PD	Pharmacodynamic
PK	Pharmacokinetic
POD	Point of Departure
POD <sub>adj</sub>	Point of Departure Adjusted
PPRTV	Provisional Peer Reviewed Toxicity Value
ppb	Part(s) per billion
ppm	Part(s) per million
RAGS	Risk Assessment Guidance for Superfund
RC	Risk Characterization
RfC	Reference Concentration
RfD	Reference Dose
RfV	Reference Value
RMEG	Reference Dose Environmental Media Evaluation Guide
TCE	Trichloroethylene
TSCA	Toxic Substances Control Act
TTD	Target Organ Toxicity Dose
UF	Uncertainty Factor
UF <sub>A</sub>	Uncertainty Factor for animal to human extrapolation
UF <sub>D</sub>	Database Uncertainty Factor
UF <sub>H</sub>	Uncertainty Factor for human variability
UF <sub>L</sub>	Uncertainty Factor for LOAEL to NOAEL extrapolation
UF <sub>S</sub>	Uncertainty Factor for Subchronic to Chronic extrapolation
VC	Vinyl Chloride
ug/L	Microgram per liter
ug/m <sup>3</sup>	Microgram per meter cubed

## 2. LIST OF OPINIONS

My opinions herein are derived from my education and experience including my knowledge of materials included in my bibliography and other materials with which I am familiar from previous endeavors. These opinions are reached with a reasonable degree of scientific certainty. My opinions in this case were arrived at using the same methodology and scientific rigor that have applied throughout my academic, professional, and consulting career performing research, authoring peer-reviewed manuscripts for publication, and assessing the scientific merit of ideas and works of other scientists through the peer review process. My approach included reviewing robust and rigorous peer-reviewed literature, regulatory standards, and other relevant literature and resources, assessing the strength of each of the sources, and weighing the limitations of the sources. I reserve the right to develop additional opinions as a need for them may arise and modify these opinions on the basis of emerging information.

Opinion 1: The policies and procedures used to develop regulatory risk values (including the Environmental Protection Agency's (EPA) Reference Dose and Reference Concentration values, the Agency for Toxic Substances and Disease Registry's (ATSDR) Minimal Risk Level values, EPA's cancer potency factor values and regulatory values including EPA's Maximum Contaminant Level values) are conservative and health protective and embody an unquantified margin of safety. These values also include various uncertainties, assumptions, and extrapolations, all of which preclude their application in demonstrating an increased risk associated with exposure.

Opinion 2: The conservative estimates of risk developed on the basis of regulatory risk values include uncertainties, assumptions, and extrapolations that limit their ability to estimate the risk to a specific individual. They are theoretical upper-bound estimates of risk that may not reflect true risk even at the population level.

Opinion 3: A cancer risk assessment does not reflect the actual risk to a population or to an individual, but rather the theoretical upper bound estimate of risk that can be used for policy-based decisions. The true cancer risk, in spite of what may be presented, may be as low as zero.

Opinion 4: The renal cell carcinogenicity of trichloroethylene is a high-dose effect. Extending the cancer potency to lower doses is recognized by EPA as a major uncertainty.

Opinion 5: There is no numerical value for a Hazard Quotient or a Hazard Index that connotes increased risk. Summing Hazard Quotient values to develop a Hazard Index value for chemicals whose mode of action is unknown or different represents a conservative decision and may artificially increase the Hazard Index.

Opinion 6: The available evidence does not support the supposition that a toxicologically synergistic interaction may occur; addition of risks is a conservative, albeit valid, approach to assess the risks of mixtures of chemicals at Camp Lejeune.

Opinion 7: In light of knowledge of the impact of metabolism on the toxic endpoints, and the advanced pharmacokinetic information describing route-specific differences in the metabolism of Camp Lejeune chemicals, comparisons of risks between routes of exposure without considering metabolism is invalid.

Opinion 8: Screening level risk assessments like the ATSDR's Public Health Assessment for Camp Lejeune Drinking Water (ATSDR, 2017a) may identify situations, chemicals, or exposures that require a further evaluation before conclusions of risk can be reliably reached. Such a further evaluation is guided by both EPA and ATSDR, but such an evaluation has not yet been conducted.

Opinion 9: Maximum Contaminant Levels are regulatory values quantified by the extrapolation of EPA oral Reference Dose values. An exceedance of the Maximum Contaminant Level value does not represent a health risk.

Opinion 10: EPA's decision to ban trichloroethylene is not based upon environmental contamination of drinking water, and is not related to the health risks from such contamination, but is from a conservative extrapolated risk from other uses of TCE that would result from significantly greater exposures.

### 3. QUALIFICATIONS

I am a Toxicologist and Risk Assessor, and Chief Scientist of Lipscomb and Associates, PLLC, located in Sherwood, Arkansas. I hold both a Bachelor of Science and Master of Science in Biology from the University of Central Arkansas and a Ph.D. degree in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences. I am a board-certified toxicologist, holding both certification as a Diplomate of the American Board of Toxicology (DABT) and recognition as a Fellow of the Academy of Toxicological Sciences (ATS).

Since 1984, I have been actively employed and involved in the area of toxicology. My initial employment was at the Food and Drug Administration's National Center for Toxicological Research in Jefferson, AR. There I conducted research in the areas of developmental toxicology, neurotoxicology, chemical metabolism, pharmacokinetics, and measuring chemical effects in vitro then determining whether they would be expressed if the chemical were exposed to the living animal.

In 1991, I was commissioned as an Officer in the U.S. Air Force and was stationed in the Armstrong Toxicology Laboratory at Wright-Patterson AFB, OH. I was Chief of the Metabolism Section where I pioneered the military's first large-scale investigation of human variability which awarded me the Air Force Achievement medal. The primary focus of my Section was on the metabolism of trichloroethylene, which was funded in part by the Laboratory, the Air Force Office of Scientific Research and the U.S. Environmental Protection Agency. I received several awards and recognition for my contributions to the peer reviewed literature and was invited to present findings of the variability of chemical metabolism among humans to the Gordon Research Conference on Drug Metabolism twice, to the European Conference on Specificity and Variability in Drug Metabolism, to the European Federation of Pharmaceutical Sciences, and to a European Meeting of the International Society for the Study of Xenobiotics. I was responsible for designing, implementing, and interpreting results from experiments with human tissues that identified the chemical metabolism values that were implemented in EPA's physiologically based pharmacokinetic models used in EPA's risk assessment that produced the cancer and non-cancer, oral, and inhalation risk values for trichloroethylene.

Following my completion of active duty in 1998, I accepted a position in EPA's National Center for Environmental Assessment in the Division in which EPA's Integrated Risk Information System (IRIS) originated. During my time at EPA, I was invited to join the Division's work in chemical mixtures, where I contributed to EPA's guidance documents on chemical mixtures and cumulative risk. I authored and co-authored several peer reviewed publications and book chapters on methods and considerations in chemical risk assessment, including chemical mode of action analysis. I was invited to present lectures and symposia on the toxicology and risk assessment of mixtures of chemicals to regional, national and international scientific meetings, and received multiple awards for my contributions to the field of chemical mixtures risk assessment. I taught in vitro-to-in vivo extrapolation and route-to-route extrapolation for dose response analysis and risk assessment including presentations internationally. Some of my contributions were to efforts specific to EPA's Superfund risk assessment program. I served as Chemical Manager in EPA's IRIS program, co-authored EPA's IRIS risk assessment for trichloroethylene and was an internal reviewer for EPA's risk assessment of tetrachloroethylene, developed several Provisional Peer-Reviewed Toxicity Value (PPRTV) assessments specifically requested by the Superfund program within EPA's Office of Land and Emergency Response and served as EPA's Program Manager for

its Provisional Advisory Level values program (largely aimed at chemical emergencies). As part of my responsibilities for EPA, I estimate that I have developed more than 100 human health risk values, many of which are in the open literature and have served as the basis for EPA decisions and regulations. I have received multiple awards from EPA for my risk assessment work, including in the areas of dose response analysis, pharmacokinetics, drinking water contaminants and chemical mixtures; among these awards is a Gold Medal for service on EPA's IRIS risk assessment for trichloroethylene. In 2016, I transferred to EPA's National Homeland Security Research Center (NHSRC) and assumed overall responsibility for its Provisional Advisory Levels (PALs) program. I have developed acute and short-term exposure guidance values for oral and inhalation exposures to hazardous substances and chemical warfare agents. I have additionally lectured in several continuing education courses taught locally, regionally, nationally, and internationally on topics of toxicology and health risk assessment. I have served as course director for a graduate course in Human Health Risk Assessment for the University of Louisville, where I am an adjunct professor of Toxicology. I have authored or coauthored 46 peer-reviewed government technical reports, 15 book chapters and 80 peer-reviewed publications. A list of my publications is included within my attached curriculum vitae. I retired from federal service in 2019.

I currently serve on the Health Advisory Board for NSF International, an organization which certifies devices, appliances, and equipment that comes into contact with drinking water. As a Board member, I review and critique the interpretation of toxicity and dose response data for specific chemicals that may be released from these products into drinking water consumed by humans. I am a full member of the American Industrial Hygiene Association, the Society of Toxicology and the Society for Risk Analysis. I serve on the Emergency Response Planning Committee of the American Industrial Hygiene Association, where I am responsible for developing guidance values for inhalation exposures and reference documents on the toxicity of specific chemicals. I have previously served as the president of the Ohio chapter of the Society for Risk Analysis as well as the Society's Dose-Response Specialty Group. I have served the Society of Toxicology on its governing council and as president of its Ohio Valley Chapter and of its Risk Assessment Specialty Section. I am also a member of the Society's Chemical Mixtures Specialty Section. I have also served as president of the American Board of Toxicology. I am currently on the Editorial Board and am a former Associate Editor for Toxicological Sciences, as well as a member of the Editorial Board and former Associate Editor for Toxicology Mechanisms and Methods and I serve on the Editorial Board for Toxicology Reports. I am an invited peer reviewer of submitted manuscripts for many other toxicology and risk assessment journals, as well. I have edited a text, Toxicokinetics and Risk Assessment (Informa, 2007), which summarized aspects of chemical toxicology and risk assessment with an emphasis on how chemical metabolism and distribution to tissues can and does influence toxicity and how such information can determine quantitative aspects of risk assessment values.

Toxicology, a blend of biology, chemistry, and medicine, is the science of the adverse effects of substances (e.g., chemicals, physical agents, and drugs) on biological systems, including the effects, the recognition, and the mechanisms of a chemical-related disease. Whether a substance is a toxicant depends upon two inseparable criteria: 1) the intrinsic nature of the substance, and 2) the dose, or how much of a substance the individual actually takes into their body. In toxicology, we study the dose-response of chemicals on biological systems, with emphasis on understanding how chemicals produce their effects. Toxicologists and risk assessors also provide expert opinions with respect to causation in toxic tort litigation. In risk assessment, we seek to understand the relationship between human exposures and the likelihood that those exposures may produce harm.

## 4. EXECUTIVE SUMMARY

EPA (1995, and elsewhere) has cautioned against reliance on numerical values, such as Hazard Quotient values, as risk estimates. That admonishment serves as the primary backdrop for this report. **Therefore, discussions of risk, based on a comparison of an exposure to a risk value, must not stop at the presentation of a numerical value.**

“[S]ince every assessment carries uncertainties, a simplified numerical presentation of risk is always incomplete and often misleading.” (EPA, 1995).

“[T]he current approach for deriving RfDs [reference doses] does not provide the risk manager with insight concerning the potential hazard posed by a chemical when exposures exceed the RfD.” (Swartout et al., 1998).

“[C]urrent RfD-based risk characterizations do not provide information on the fraction of the population adversely affected by a given dose or on any other direct measure of risk.” (EPA 2000a).

“MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects.” (ATSDR, 2019a).

“Reference values are not predictive risk values; they provide no information about risks at higher exposure levels.” (EPA, 2022a).

“The HI [hazard index] cannot be translated to a probability that adverse effects will occur, and it is not likely to be proportional to risk.” (NRC, 2009).

“Because of the uncertainties and conservative assumptions inherent in deriving the cancer slope factors, this is only an estimate of risk; the true risk is unknown and might be as low as zero.” (ATSDR 2017a).

ATSDR’s Public Health Assessment for Camp Lejeune Drinking Water (PHA) (ATSDR, 2017a) is a screening level analysis, as described by ATSDR (2005), and so is designed to identify chemicals and exposures that warrant further evaluation.<sup>1</sup> The PHA is an incongruous collection of statements that makes the inference of quantitation of risk impossible. ATSDR states that the PHA was conducted to evaluate whether past exposures to several chemicals “were likely to have resulted in adverse health effects” (ATSDR, 2017a, p. ix). Using the health conservative upper end exposure estimates developed by ATSDR, ATSDR engaged in an “Environmental Data Screening Process” (ATSDR, 2017a, p. 6). For these “estimated levels” of exposure, ATSDR acknowledges exposure related data gaps (ATSDR, 2017a, p. 43):

- Lack of accurate exposure concentrations for chemicals,
- Lack of exact knowledge of exposure durations, and

---

<sup>1</sup> The PHA’s Conclusion 5 regarding lead is beyond the scope of this Report.

- Lack of information for site-specific data for water consumption, particular data for showering/bathing and human body weights.

ATSDR also identified data limitations for chemicals encountered at Camp Lejeune (ATSDR, 2017a, p. xix). For these, “ATSDR chose conservative (health-protective) data interpretation options” to complete the screening analysis (ATSDR, 2017a, p. xix). ATSDR identified these limitations:

**Limitations related to VOCs include the lack of water sampling data prior to 1982, uncertainty about when contamination first occurred in water supplies, reliance on the testing of finished water for leaving the treatment plant rather than at the point of exposure (i.e. the faucet or shower) for estimating exposure, limited information about site-specific exposure parameters, lack of indoor air samples, uncertainties that are intrinsic to the use of models to predict inputs to the assessment, uncertainties about the combined effects of exposure to the specific mixture of chemicals in the water systems, limitations in the available toxicological data to predict the health impacts of exposure, and lack of specific health outcome data, specifically incidence data for cancer and cardiac defects to confirm the potential effects that are described in this assessment.**

ATSDR’s stated purpose of screening for the potential effect of their estimated exposures was “[t]o identify contaminants that required further investigation.” (ATSDR, 2017a, p. 6). The ATSDR’s exposure estimates were combined with “Comparison Values” that included ATSDR Minimal Risk Level (MRL) values, EPA oral Reference Dose (RfD) values, EPA Inhalation Reference Concentration (RfC) values, EPA cancer Oral Slope Factor (OSF) values, and EPA cancer Inhalation Unit Risk (IUR) values (ATSDR, 2017a, p. 6). These values were translated into other Comparison Values<sup>2</sup> (CVs) that included Environmental Media Evaluation Guide (EMEGs), Reference Dose Media Evaluation Guide (RMEGs), and Cancer Risk Evaluation Guide (CREGs) based on an accounting-for the volume of air breathed and water ingested daily (ATSDR, 2017a, p. 7). Additional values used as points for comparison were Maximum Contaminant Levels<sup>3</sup> (MCL) and Maximum Contaminant Levels Goal (MCLG) values. In discussing “ATSDR’s Screening Analysis”, the PHA acknowledged, “[a]s health-based thresholds, CVs are set at a concentration below which no known or anticipated adverse human health effects are expected to occur.” (ATSDR, 2017a, p. 78). Consistent with the definitions for the underlying values, this comparison provided a context for exposure, which should not be misconstrued as actual “risk” to individuals:

---

<sup>2</sup> Of Comparison Values, ATSDR (2005) writes, “[c]omparison values are not thresholds of toxicity. Comparison values should not be used to predict adverse health effects. These values serve only as guidelines to provide an initial screen of human exposure to substances. Although concentrations at or below the relevant comparison value may reasonably be considered safe, it does not automatically follow that any environmental concentration that exceeds a comparison value would be expected to produce adverse health effects.”

<sup>3</sup> MCL values for drinking water chemicals are found in EPA (2018).

- Regarding the use of MRL values to estimate risk, ATSDR has repeatedly advised against such, including: “MRLs are set below levels that might cause adverse health effects in most people, including sensitive populations.” (ASTDR, 2005).
- Regarding the use of Reference values to estimate risk, EPA has repeatedly advised against such, including: “Reference values are not predictive values; they provide no information about risks at higher exposure levels.” (EPA, 2022a).
- ATSDR (2017a) has written, “Because of the uncertainties and conservative assumptions inherent in deriving the cancer slope factors, this is only an estimate of risk; the true risk is unknown, and might be as low as zero (ATSDR 2005).”
- Comparison Values (CVs) are not thresholds of toxicity. CVs should not be used to predict harmful health effects. CVs are based on a default exposure scenario and do not reflect site-specific exposures. These values serve only as guides to provide an initial screen of human exposure to contaminants.<sup>4</sup>
- For carcinogens, MCLs are set as close to MCL-G values as practically possible, considering laboratory analytical sensitivity and the cost of chemical analysis. For non-carcinogens, the MCL is set at a concentration that delivers one-fifth of the daily oral reference dose. MCL values are regulatory standards, but their exceedance does not automatically imply risk (EPA, 2018).

The risks associated with chemicals evaluated in screening approach applied in the PHA by ATSDR in 2017 were identified based on MRL values developed by ATSDR and non-cancer reference values and cancer slope factors developed by EPA (ATSDR, 2017a). Values for vinyl chloride were available from ATSDR (2006 and 2024) and EPA (2000a); for tetrachloroethylene (PCE) from ATSDR (1997 and 2019b<sup>5</sup>) and EPA (2012c); for trichloroethylene (TCE) from ATSDR (1997 and 2019a) and EPA (2011a); for dichloroethylene from ATSDR (2023) and EPA (2010a, b); and benzene from ATSDR (2007) and EPA (2000b). For some chemicals, ATSDR has adopted EPA chronic reference values. However, the PHA failed to adequately identify the sources of risk values used in its approach to develop Hazard Quotient and Hazard Index values for these chemicals. This prevents a fair and more complete evaluation of the implications of Hazard Quotient and Hazard Index values presented by ATSDR.

The PHA (ATSDR, 2017a, p. 78) itself clarifies the screening application of the exercise and describes the use of Comparison Values, “to determine which chemicals to examine more closely” and wrote that “Exceeding a CV does not mean that health effects will occur, just that more evaluation is needed.” If the exposures exceed these guideline values and further evaluation is needed, the PHA (ATSDR, 2017a, p. 79) advised that “[a] direct comparison of site-specific exposure and doses to study-derived exposures and doses that cause adverse health effects is the basis for deciding whether health effects are likely or

---

<sup>4</sup> [https://www.atsdr.cdc.gov/pha-guidance/conducting\\_scientific\\_evaluations/screening\\_analysis/screening\\_levels\\_used\\_by\\_atsdr.html](https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/screening_analysis/screening_levels_used_by_atsdr.html)

<sup>5</sup> Public review drafts for PCE and TCE were released in 2014, which precedes the 2017 Public Health Assessment.

not.” The PHA developed non-cancer Hazard Quotient values by comparing a chemical’s estimated high-end exposures to their respective MRL or Reference values, and provided a risk-based interpretation (ATSDR, 2017a, p. 29), writing, “[t]he HI data indicate higher health risk at Hadnot Point than at Tarawa Terrace across all age groups.” However, this interpretation of “risk” goes against the definitions and intended application of MRL values, Reference values and Hazard Index values. An examination of the PHA’s “Discussion of Non-cancer and Cancer Health Effects” (ATSDR, 2017a, pp. 25-33) reveals no indication that ATSDR went further into any comparison of human site-specific exposures to “study-derived exposures and doses that cause adverse health effects.” In contrast, in evaluating Camp Lejeune, the National Research Council (NRC, 2009) conducted an exposure assessment and made such a comparison. The NRC reported, “[t]he lowest doses at which adverse health effects have been seen in animal or clinical studies are many times higher than the worst-case (highest) assumed exposures at Camp Lejeune.” (NRC, 2009). For this and other reasons it should be clear that ATSDR’s PHA does not indicate that any individual risk is likely and to interpret it otherwise would be misleading.

In reaching its conclusions about cancer risk, ATSDR took a health conservative approach and acknowledged that “[b]ecause of the uncertainties and conservatism inherent in deriving [cancer slope factors] and [inhalation unit risk values], this is only an estimate of risk; *the true risk is unknown and could be as low as zero* (USEPA, 2003a).” (ATSDR 2017a) (emphasis added). As much as ATSDR’s Public Health mission extends to issues surrounding the release of potentially toxic chemicals to the environment, Camp Lejeune stands out as a National Priority List (i.e., Superfund) site. EPA’s Risk Assessment Guidance for Superfund (RAGS) guides how to evaluate risks at Superfund sites. Such guidelines should be taken into consideration.

Additionally, drinking water contamination is governed by the Safe Drinking Water Act. Regulations, including MCLs, are based on health conservative assumptions incorporated in the respective statutes and decision-making process. Similarly, EPA’s decision to ban TCE is governed by the Toxic Substances Control Act (TSCA) and is not based upon environmental contamination of drinking water. Risk assessments conducted and decisions made under the TSCA have no bearing on the issues faced at Camp Lejeune.

This Expert Report presents a number of issues important in risk assessment relative to the assumptions, uncertainties, and extrapolations required to develop risk values and to interpret the implications of exposures evaluated in the context of those values.

Because the risk values against which the potential effects of chemicals are judged are based on the responses at the biochemical, cellular, or organism level, this Report opens with a review of biology and how chemicals can produce biologically relevant alterations and how to know if an alteration is really biologically relevant. How the assumptions, uncertainties, and extrapolations are handled in developing these risk values ensures a level of health conservatism and contributes to the margin of safety present in the derived values. An important aspect of the MRL values and non-cancer Reference values is that they do not address the dose response aspect – they provide no information on the likelihood of effects when exposures exceed their values. The information contained in this Report should be kept in mind when interpreting a conclusion of increased risk is based on the comparison of an estimated exposure to risk value that embody a margin of safety.

## 5. BIOLOGY AND TOXICOLOGY

It is important to understand certain aspects of biology and toxicology critical to the performance of risk assessments and the derivation of particular values in the risk assessment process.

The body is organized into organ systems, in which several different organs or tissues may act together to maintain proper function. For example, blood pressure is maintained through tissues called baroreceptors sensing pressure and transmitting responses through nerves to a part of the brain which in turn relays nerve impulses to the blood vessels and the heart to make adjustments of vascular compression, heart rate, and heart muscle contractility to adjust blood pressure in the right direction. Altering one of these tissues can alter blood pressure, or the change can be compensated by other components of the system. Measuring (detecting, demonstrating) a change in one of these parameters might not result in a change in blood pressure. Likewise, the cells in the various tissues of the body are each different, containing different types and amounts of proteins, enzymes, receptor molecules, and even different types of membranes surrounding the cells themselves.

The tissues of the body are many and varied, to take care of functions like the exchange of gases between blood and air (lung tissue), voluntary movements of limbs (skeletal muscle), involuntary pumping of blood (heart muscle), learning and memory (brain), removal of waste chemicals from blood (kidney), the production of blood cells (bone marrow), the metabolism of chemicals (liver), the processing of sound waves into “hearing” (inner ear tissues), etc. To provide these varied functions, the body’s tissues are made of different types of cells, and these different cells function differently because of the different proteins and other molecules that they contain. Each cell type in the body has a specific function, enabled by the unique biochemical and molecular attributes of that cell type. These biochemical and molecular processes act together in pathways that must remain intact for the cell to function normally. *When chemicals reach the cells at concentrations sufficient to perturb these processes, then the cell can no longer maintain proper function. This difference in biochemical and molecular processes between cell types and tissues is why some chemicals affect only a certain tissue, and often only a certain cell type within a certain tissue.*

### 5.1. Environmental Concentrations are Not Exposure; Exposures are Not Doses; Doses are Not Tissue Concentrations.

Under some circumstances, chemicals can damage the cells and tissues of the body. Toxicologists study how chemicals can, and the doses that do and that do not affect cells, tissues, and organs. Therefore, it is important to separate “exposures” from “doses.” Exposures can be thought of as contact with an environmental medium (e.g., air, drinking water<sup>6</sup>) that contains the chemical. The absorbed dose is the amount of contacted chemical that is taken in by the body. This absorbed amount is usually called a dose and is usually expressed in units of milligrams of the chemical taken in per kilogram of body mass

---

<sup>6</sup> It is important to distinguish reported concentrations relative to whether they are in source water, ground water, well water, or tap water. Of these, only tap water (or drinking water) is supplied for human consumption.

per day (mg/kg/day). But, for the chemical to cause an effect, whether a “good” effect or a “bad” effect, it must survive metabolism by the liver, being “blown off” by the lungs, or being eliminated by the kidney through the urine. Even then, it must finally reach the target tissue (like the heart, kidney or bone marrow) – and reach the tissue at levels high enough and for long enough to produce the effect. Metabolism occurs primarily in the liver, which is an important condition relative to evaluating risk from exposure via the skin, inhaled air, or by oral ingestion. One hundred percent of the chemical absorbed from an oral exposure goes first to the liver and then the rest of the body, but this is not true for skin or air exposures. This makes a comparison of doses and effects on the basis of an exposure from air versus an exposure from an oral dose unreliable, especially when a toxic effect is caused by a chemical metabolite. This is because it is the tissue concentrations of the toxicologically active form of the chemical (e.g., a metabolite) that mediates the responses.

## 5.2. Cells and Tissues Respond to Stimuli to Maintain Homeostasis

Once enough chemical reaches the target tissue, the cells begin to respond, showing the first of several individual changes which are required to produce the bad (“adverse”) effect. As the chemical concentration in the tissue increases further, additional changes occur which bring the cellular effects closer to being “adverse.” If the chemical concentration does not increase to this point, the cells undergo what is called an adaptation. Through this adaptation the normal function of the cell is maintained – there is no adverse condition. However, if the chemical concentration continues to increase, then the normal compensatory mechanisms can be overcome, and the cells and tissue may be changed to a point that an “adverse” condition may develop (NRC, 2007a).

Because many changes can be measured, ranging from those at specific types of cellular molecules known not to be adverse, to those measurements made at the functional level (like the ability to absorb oxygen through the lungs), EPA advises toxicologists to describe biological significance and the directness of the relationship between the change that they measure and the biological function (the “apical endpoint”) upon which a condition of “adversity” is implied (EPA, 2022a). Thus, changes and especially changes observed in mechanistic studies, should not be automatically assumed to be adverse.

Consider the delivery of oxygen to the tissues by blood. Red blood cells contain hemoglobin, which is the molecule that oxygen binds to in order to be carried from the lungs to the tissues. It follows that changes to hemoglobin can reduce the ability of blood to carry enough oxygen to tissues. However, cigarette smokers and individuals exposed to some chemicals (at some doses) can also experience damage to hemoglobin. As an example, the National Academy of Sciences assessed the risks of aniline, a chemical used in the dye industry, and indicated that a 20% change in human hemoglobin<sup>7</sup> from exposure to the chemical did not result in symptoms from low levels of oxygen (NRC, 2007b).

Another example, which relates to functional reserve capacity, is male sperm count and the ability to fertilize an egg. Sperm count is a “continuous variable”, meaning that sperm count can have any value,

---

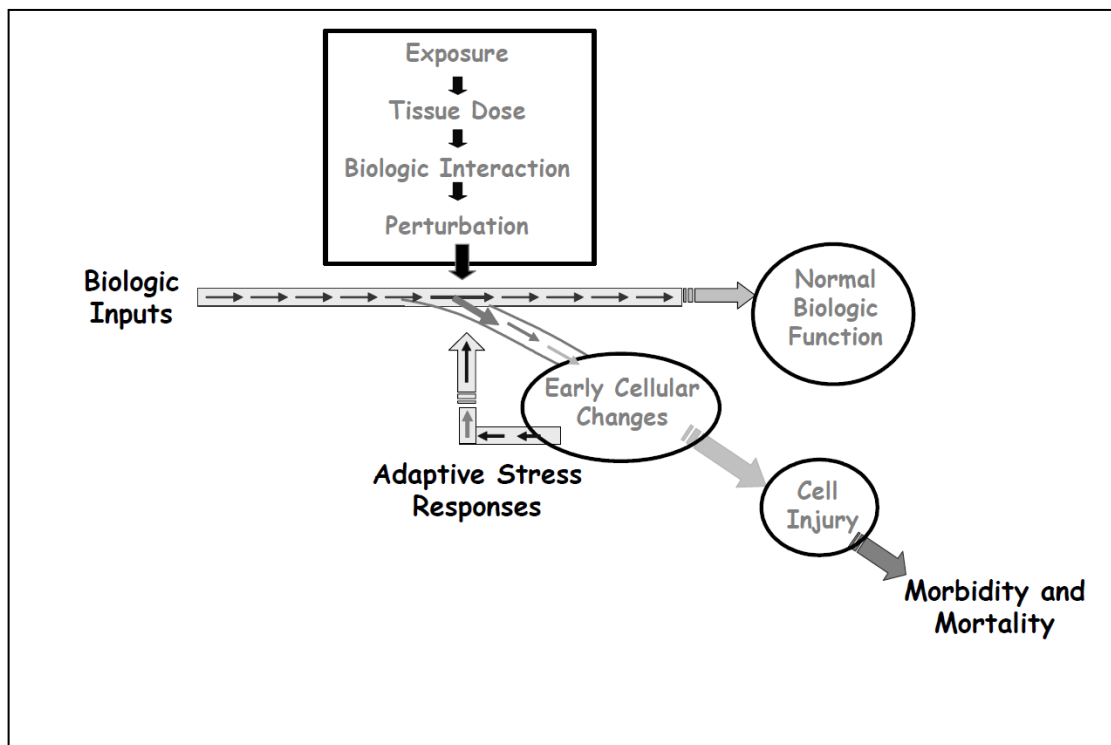
<sup>7</sup> NRC (2007) Acute Exposure Guideline Level for Aniline wrote, “A review of the published data indicates that methemoglobin levels of 15-20% in humans results in clinical cyanosis but no hypoxic symptoms.”

and sperm count varies among males. Having a “good” sperm count increases the likelihood of fertilization and having a “low” sperm count decreases that likelihood, but a lower-than-average sperm count does not eliminate the possibility of fertilization entirely. While it follows that decreases in sperm count at some magnitude might result in decreased fertilization, there is a natural plethora of sperm cells, and a normal range of values, and so not all reductions of sperm count result in decreased ability to fertilize. So, not just the statistical significance, but also the biological significance of the change must be considered.

Moreover, it is not just the magnitude of a change that is important in demonstrating an “adverse” effect. The type of change is also important to consider. The body’s cells and tissues have an innate ability to repair themselves to compensate for changes and maintain normal function. When cells get damaged, the tissue repairs them; when cells get old and die, the tissue replaces them. Likewise, normal function in the face of stress, including chemical exposures, is maintained through responses at the cellular and tissue levels.

The National Research Council (NRC, 2007a) addressed innovations in toxicity testing, through which the concept of the Toxicity Pathway was solidified (Figure 1, below). This distinguishes exposures of chemicals that may or may not produce early cellular changes from exposures that exceed a threshold, and above which may result in cell injury. The Toxicity Pathway demonstrates that tissue doses can be followed by biologic interactions, which can be followed by perturbation, which can be followed by early cellular changes. Early cellular changes can then lead to either adaptive stress responses and maintenance of normal biologic function, or early cellular changes may be followed by cell injury, depending on the dose.

**FIGURE 1. The Toxicity Pathway.**



**FIGURE 1. The Toxicity Pathway.** (NRC, 2007). *This figure demonstrates the multiple interactions and the progression of observable effects that can, under some circumstances, lead to cell injury, morbidity, and mortality (as adverse effects). It demonstrates that biological perturbations (which may be measurable events) occur upstream of adverse effects.*

NRC (2007) states, “[w]hen perturbations are sufficiently large or when the host is unable to adapt because of underlying nutritional, genetic, disease, or life-style status, biologic function is compromised, and this leads to toxicity and disease.” Needless to say, NRC (2007) recognized that some perturbations may not be large enough to compromise biological function, which can lead to toxicity. Effectively, NRC (2007) distinguishes among the concepts of perturbation, biological function and toxicity. EPA’s Framework for Human Health Risk Assessment (EPA, 2014a) describes this continuum of events: “[f]or example, at low exposures, some systems will remain within their homeostatic limits, while at higher levels of stress, adaptive biologic responses may occur, the adversity of which may depend on the physiological characteristics of those exposed; that is, groups of sensitive individuals may respond adversely, whereas others may not. At still greater magnitude of stress, the adaptive capacity may be overwhelmed for all groups, increasing the likelihood of adverse effects.”

### 5.3. Biological Response is the Result of a Particular Toxicity Pathway

As shown above in the Toxicity Pathways, a biologically adverse effect does not start and end with a single event. This series of linked biochemical or cellular events is called a mode of action and the understanding of specific biochemical events associated with the disease can lead to developing an ordered progression or chain of events that leads to the ultimate health effect – the disease. But putting together a pathway does not mean it is complete, correct, or applicable to the range of doses a human might be exposed to (Boobis et al., 2006, 2008). Proposing the mode of action (the pathway from exposure to effect) often involves information from studies conducted outside the body, using pieces of cells or isolated molecules that may be exposed to concentrations of chemicals that may not be found in an exposed human or animal. The individual biochemical events measured may form a chain of events where the individual events become expressed as doses increase or as time progresses. The events that are necessary to produce the health effect are called key events,<sup>8</sup> but not all events that can be measured are key events.

---

<sup>8</sup> Whether an event is “real” is an important aspect of mode of action development. Plaintiffs’ Expert Dr. Miller indicates that a specific chemical, abbreviated as TaClo, shown under some conditions to inhibit mitochondrial function in a brain region affected by Parkinson’s Disease, is a metabolite of TCE. However, Plaintiffs’ Expert Dr. Cannon wrote, “While there is some controversy on whether TaClo is formed in mammals exposed to chloroethylenes, there are reports of detection in the blood of humans exposed to known chloroethylene metabolites [Bringmann et al., 1999].” However, I am not aware of any subsequent studies that have confirmed the formation of TaClo from TCE in animals or humans.

Some events may not be necessary to the disease outcome. They may be offshoots of the process, which are in effect dead-end processes, or they may result from (rather than) cause the disease.

Necessary testing of proposed modes of action requires careful development of whole animal experiments to determine whether they actually operate under real world conditions. And, sometimes the individual events proposed in the mode of action may be observed in whole animal studies, but at doses not relevant to human exposures (EPA, 2014b), meaning that those events would not be produced following exposure to lower doses (Bus, 2017; Slikker et al., 2004).

For these reasons, basing a risk assessment on the finding of an isolated biochemical event that is not the ultimate health effect is uncertain, and adds a level of conservative health protection to the risk value developed.

#### 5.3.1. Not all changes are adverse.

EPA characterizes “adversity” as an altered ability to function. Functional impairment requires a multi-step process that includes discrete intermediate biochemical processes that can be measured. But measuring effects on these processes is not the same thing as measuring an effect on the function of an organ. While these intermediate processes may be necessary for the overall system to function, some levels of change in intermediate processes may not be biologically significant, or may not change the function of the cell or organ (EPA, 2022a).

If the measured event occurring at an identified dose does not itself represent a functional impairment, there is uncertainty that the identified dose will result in a functional impairment. And, it should not be assumed that the doses that produce a given magnitude of change in the measured event will produce a corollary magnitude of change in the biological function. Not all changes impact function.<sup>9</sup> Without biological confirmation, assuming that the change in the measured intermediate event represents an adverse effect is a health conservative assumption.

---

<sup>9</sup> An example is provided by considering the metabolism of TCE and the dependence of TCE’s toxicity on chemical metabolites (EPA, 2011a). It was shown that because of several factors, including the limitations imposed by the human body, the limiting caused by absorption and distribution, and because of the highly effective nature of the enzyme CYP2E1’s capacity to metabolize TCE, the real-life difference, “the functional impact” of a 600% difference in a measured biologically relevant parameter (CYP2E1 enzyme activity) was only 2% functional impact. The TCE had to be absorbed into the blood stream, then delivered in the blood to the liver and move from the blood to the liver by chemical partitioning, and *then* be available for metabolism.

## 6. WHAT IS RISK ASSESSMENT?

Based on the principles of biology and toxicology discussed above, one can perform a “risk assessment.” A toxicological risk assessment can derive values that provide information about toxicological risks. It is critically important to understand how those values are derived and used when evaluating their application to given circumstances. In particular, a value derived from a risk assessment rarely represents the actual risk. In the context of toxicological risk assessment, as described in detail below, the values derived apply certain health-protective assumptions so that the actual risk is, in all likelihood, well below the risk represented by the value derived.

We perform risk assessments daily. Basically, all risk assessments start with “What if...?” For example, “What if I exceed the speed limit in a residential neighborhood by 10 miles per hour?” While the benefit of more speed increases the possibility of getting somewhere sooner, the whole picture needs to be considered, and that picture includes the potential consequences of speeding, including the increased likelihood of an accident. Risk assessment is the comparison of the likelihood and magnitude of the benefits of an action or decision against the likelihood and magnitude of the potential consequences of that action or decision. In comparing the potential benefits to the potential consequences and likelihood of a decision or action, human health risk assessment is no different.

The operative question then is “If I do this, what will happen?” And, so, we need to characterize what is the “this” (“If I do this ...”), and we need to characterize the “what” (“...what will happen?”). In human health risk assessment, the “this” is a chemical exposure and the “what” is the potential likelihood and magnitude of the health impact. Here, the question is “What is the magnitude and likelihood of the potential consequences associated with exceeding a chemical exposure guidance or health standard value?”

Accordingly, risk assessment is an iterative four-step process that provides information on the probability of adverse effects following chemical exposures (NRC, 2009):

- Hazard Identification (HI) identifies adverse effects posed by exposure.
- Dose Response (DR) quantifies the relationship between dose and effect.
- Exposure Assessment (EA) assesses exposure pathways, outcomes, and populations.
- Risk Characterization (RC) integrates information from HI, DR, and EA to generate an estimate of the overall risk to human or environmental health.

### 6.1. The Likelihood of an Effect or Response is a Function of Exposure or Dose.

*All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy. Paracelsus (1493-1541).*

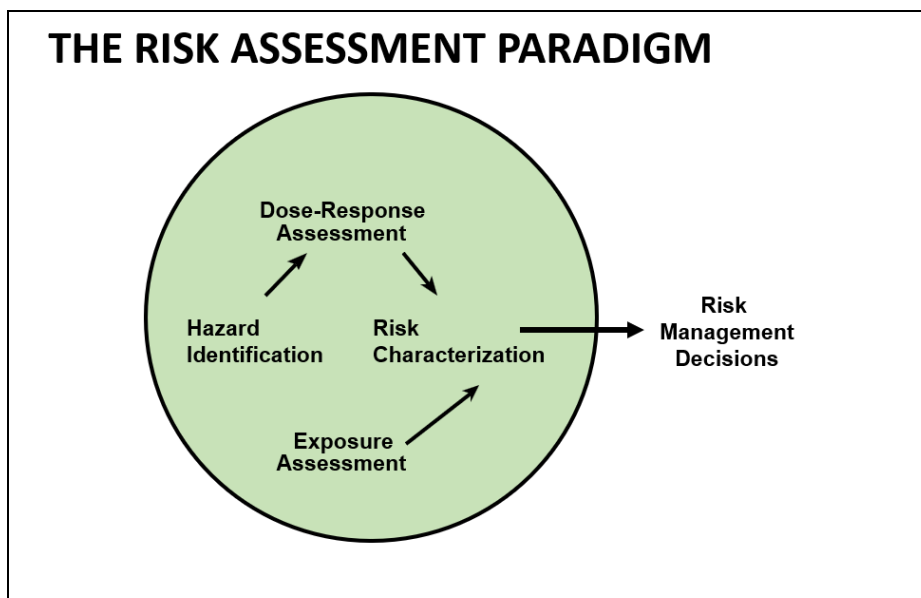
This concept was put in the context of toxicology long ago and is often found in the opening pages of toxicology texts. It is as true today as then. Risk depends on the potency of the chemical and the magnitude of exposure. The fundamental equation for human health risk assessment is:

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

And a fairly common thing to do is to compare a reconstructed estimate of a potential past human exposure to a health-conservative, protective guidance value or exposure standard to infer risk or causation. For example, one may try to compare a reconstructed estimate of exposures to chemicals in drinking water at Camp Lejeune to EPA's current regulatory maximum contamination level or oral reference dose for that contaminant in drinking water. In fact, such a comparison has been done by the ATSDR and Plaintiffs' Experts in this case without a full discussion of the issues. However, EPA itself has cautioned against drawing conclusions about risk and causation from such comparisons without also accounting for the uncertainties involved (EPA, 1995, 2000c).

To guide the process of risk assessment, the National Research Council (NRC, 1983) put together the Risk Assessment Paradigm, which provides a four-step structure for conducting human health risk assessments. It looks like this:

**Figure 2. The Risk Assessment Paradigm.**



**FIGURE 2. The Risk Assessment Paradigm.** Adapted from NRC (1983). Moving from left to right, the first step is Hazard Identification, where human epidemiologic and animal experimental studies are evaluated to identify the types of effects that are associated with exposure to the chemical, irrespective of the level of the exposure or dose. It "bounds the universe" of effects for quantitative consideration. The next two steps are Exposure Assessment (not covered in this report) and Dose Response. The Dose Response Assessment more deeply evaluates information for the types of effects identified to determine which doses are and which doses are not associated with the health effects identified. It culminates with the development of conservative, health protective non-cancer oral reference dose, inhalation reference concentration, and oral and inhalation cancer slope factor values (risk values for dermal exposure are not developed by EPA or ATSDR). This is done remembering the central tenet of Toxicologists worldwide: Whether the substance is toxic depends on the dose.

And, so, there are three steps to quantify risk and one step to characterize risk:

- the Hazard Identification step identifies health effects for evaluation;
- the Dose Response Assessment step develops risk values;
- the Exposure Assessment step characterizes the doses associated with a specific exposure, and
- the Risk Characterization step combines the results of the exposure assessment step with the results of the dose response assessment step to place the exposure in the context of risk; and discusses the assumptions, extrapolations, and uncertainties in the process.

## 6.2. Risk Values

Thus, the risk assessment process comprises two separable processes. The first process develops the risk values for the chemicals of interest, such as an EPA Reference Dose or ATSDR MRL value. However, developing a risk value is not risk assessment, in that there is no “exposure” context. Agencies develop risk values on the basis of science policy and quantitative methods, which can and do differ between agencies (Holman et al., 2017a, b). And different agencies (and different parts of the same agency, even) practice risk assessment differently. So, for a given site, like a Superfund site, it is important to use risk values, policies, and practices that are pertinent to the type of site, from the agency or part of the agency that is responsible for that activity. The risk values used in risk assessments are developed to be health protective, in other words, “conservative.” That means that they overestimate risk. This is accomplished through science policy directives and choices which guide and accompany many decision points along the risk value development process.

## 6.3. Exposure Assessment

The second process characterizes doses associated with the human exposure of interest, places them in the context of risk values, and characterizes the results in light of the assumptions, extrapolations, and uncertainties inherent in the risk value and the exposure estimate.

Risk assessments estimate the risk of scenario-specific exposures. They are undertaken to estimate whether there is cause for concern and/or additional activities. Different types of quantitation are done for non-cancer and cancer effects. For non-cancer risk assessments, these assessments cannot quantify the risk of an exceedance, but can determine whether an exposure exceeds a reference value. For cancer risk assessment, typically, the risk of an exposure is estimated, and compared to a range of acceptable risk levels.

The following sections of this Report describe the process for developing risk values for non-cancer effects and cancer effects. This Report also describes some of the health conservative policies, methods, and decisions that provide the level of health protection in risk values.

The risk assessment process ensures that risk from exposures at or below these values is not expected, but at the same time it is recognized

that these risk values cannot be used to indicate that risk is present if the exposure exceeds the risk

Risk assessments are decision-making tools, not precise analyses of actual or measurable risk, so their focus should remain on how best to inform the ultimate goal—risk reduction—rather than on generating complex distributions of possible risk estimates.

- CRARM, 1997

value. The following sections of this Report describe how chemicals affect the body and how the body responds as well as the methods for planning, conducting, and interpreting risk assessments.

## 7. RISK ASSESSMENT IS NOT A MEASURE OF TRUE RISK BECAUSE OF THE HEALTH CONSERVATIVE ASSUMPTIONS INVOLVED

A toxicological risk assessment does not represent a true measure of risk. Instead, it applies certain health protective assumptions so that the true risk is, in all likelihood, well below the values derived in the risk assessment. This applies to all of the risk assessment values that might be referenced with respect to Camp Lejeune, including the Reference Concentration Values, the MRLs, and the MCLs.

ATSDR's PHA was conducted as a screening exercise (ATSDR, 2017a). This means that ATSDR employed worst case scenarios. When data for a certain point was not available, ATSDR filled this data gap with an estimated value based on high-end upper bound values that were intended to make the results higher, and indicative of a higher level of risk than they likely were. For example, when data describing the concentration of chemicals in indoor air were not available, ATSDR filled this gap with an estimate based on high-end upper bound values that were intended to make the indoor air concentration higher. That is acceptable for a screening exercise, but it must be explained relative to real-world expectations when the screening results are discussed. ATSDR included an incomplete treatment of this topic in a one-page section that does not address the limitations produced by data gaps in the risk (comparison values) or in the toxicity studies upon which the comparison values are developed. Instead, these risk values are taken by ATSDR to represent "gospel" and used without further evaluation. From this, ATSDR has not presented anything near a complete listing of the data limitations inherent in its screening exercise.

In fact, ATSDR presented the work as a screening analysis conducted "to determine which chemicals to examine more closely" (ATSDR, 2017a, p. 78). ATSDR said they used comparison values (CV) "to screen contaminants for further evaluation." This specifically does not mean that the results are reliable as indicators of increased risk. ATSDR makes this perfectly clear in the PHA, writing, "[e]xceeding a CV does not mean that health effects will occur, just that more evaluation is needed." (ATSDR, 2017a, p. 78) However, and unfortunately, the results of ATSDR's screening analysis presented in the PHA seem to have been given more weight than even ATSDR may have intended. As a matter of fact, the results of the screening analysis have not yet been extended by further evaluation as ATSDR advised.

EPA discusses the roles of planning and scoping, and risk characterization, writing, "[p]lanning and scoping can be viewed as a lens that defines the purpose and scope of a risk assessment and focuses the issues involved in performing the assessment. The risk characterization portion of the assessment, in turn, is a second lens that focuses the conclusions of the risk assessment into a coherent picture for applying and communicating the assessment." (EPA, 2000c). Avoiding over- and/or mis-interpretation of the findings in a risk assessment can be avoided if it is kept in mind that "[t]he degree to which confidence and uncertainty are addressed [in the interpretation of findings] depends largely on the scope of the assessment and available resources." (EPA, 1992). Unfortunately, Planning and Scoping documents or sections are not available for many EPA/IRIS assessments, in which reference values and

cancer potency factors are derived.<sup>10</sup> Recently, EPA (2022a) has described the Planning and Scoping activity of its IRIS assessment, in which the first three key science issues to be addressed are:

- Human relevance of findings in animals
- Whether an endpoint is considered adverse or adaptive
- Issues where conflicts in the evidence are known, including hypothesized modes of action that lack scientific consensus

While EPA identifies these as key issues, under the conservative approach to risk assessment applied for EPA's IRIS values, decisions of the human relevance of a mode of action based on findings in animals or in vitro are based on assumption of relevance unless it can be demonstrated that alternative (untested) modes of action may be operative, that an endpoint is or could become adverse, or an endpoint may be an indicator (a marker) for an adverse effect. This cuts closely to the conservative nature of EPA risk assessments, but here supports an understanding of the purpose for which reference values are derived. The intended purpose and intended application drive certain choices, like these, in risk value development (Lipscomb, 2019).

At the highest level it is important to consider that “[t]he mission of EPA is to protect human health and the environment.”<sup>11</sup> EPA develops regulations to fulfill this mission and EPA's risk assessments (i.e., IRIS assessments) are designed, conducted, and reported to provide support for risk (toxicity) values that are, themselves “protective.” EPA's risk values embody a level of conservatism and include an “adequate margin of safety” resulting in an inability of reference values to confirm that there is risk at exposures that exceed those doses or concentrations, or to quantify risk in the event of an exceedance of the reference value. To fulfill the goal “to protect human health,” EPA bases its reference values on exposures that are not accompanied by increased risk: EPA identifies or extrapolates findings to identify a no-effect level – and then extrapolates that no-effect level to even lower doses. EPA has directly addressed this in the most unambiguous of terms, stating specifically what these reference values *are not intended for*:

“Reference values are not predictive risk values; they provide no information about risks at higher exposure levels.”

EPA (2022a)

Similarly, ATSDR's stated mission is to “protect[] communities from harmful health effects related to exposure to natural and man-made hazardous substances.”<sup>12</sup> Taking into consideration this mission as

---

<sup>10</sup> Planning and Scoping documents do exist for EPA assessments conducted under the Toxic Substances Control Act (TSCA) program, but TSCA program activities are not included in EPA's management of Superfund sites.

<sup>11</sup> <https://www.epa.gov/aboutepa/our-mission-and-what-we-do>

<sup>12</sup> [https://www.atsdr.cdc.gov/about/?CDC\\_AAref\\_Val=https://www.atsdr.cdc.gov/about/mission\\_vision\\_goals.html#cdc\\_about\\_cio\\_mission-our-mission](https://www.atsdr.cdc.gov/about/?CDC_AAref_Val=https://www.atsdr.cdc.gov/about/mission_vision_goals.html#cdc_about_cio_mission-our-mission)

well as the limitations of EPA's risk values used in the PHA, ATSDR notes that "[e]xceeding [the reference value] does not mean that health effects will occur, just that more evaluation is needed." (ATSDR 2017).

And, so, the intended application of reference values is to identify exposures that avoid risk. This is the purpose to be kept in mind as the results of a comparison of exposures to reference values is characterized, for example when interpreting the PHA.

## 8. CONSERVATIVENESS OF RISK ASSESSMENT QUANTITATIVE METHODS

“Risk assessment” as a term covers activities including both the derivation of the risk (toxicity) value and the application of that value to exposure scenarios to estimate whether risk is unlikely or potentially possible.

There are two broad categories of health effects: non-cancer and cancer. As described below, EPA develops non-cancer oral reference dose values and inhalation reference concentration values; ATSDR develops non-cancer oral and inhalation MRL values, below which risk is unanticipated.<sup>13</sup> However, none of these values quantify risk if exposures exceed their values. As EPA has stated, “Reference values are not predictive risk values; they provide no information about risks at higher exposure levels.” (EPA, 2022a).

“Reference values are not predictive risk values; they provide no information about risks at higher exposure levels.”  
- EPA (2022a)

### 8.1. What does “Conservatism” Mean?

Conservatism means to err on the side of caution and can be imported into the steps of the risk assessment process. For example, this is done in the Dose Response Analysis and Exposure Assessment steps of risk assessment, which comprise the quantitative aspects of risk assessment. The dose response analysis step includes the processes of identifying the critical effect, identifying the point of departure and downwardly extrapolating the point of departure to develop a risk value. Conservatism can include erring on the side of caution in sometimes assuming that a measured biological response represents the disease or occurs at the same dose as the disease occurs. Conservatism can also include assuming that the point of departure represents the lowest of the possible doses at which the response will occur in the experiment or even that the point of departure is below the dose at which the response will occur in the experiment.

Further, the Exposure Assessment step is an exercise to estimate the exposure to be evaluated. When exposures have not been quantified through actual analysis of the exposure (as is the case for the PHA), data gaps and uncertainties exist. Some of these include the amount of contaminated water consumed, the amount of contaminated air breathed in, the number and the amount of contaminants exposed to skin, the duration (hours, days, months, years) of the exposure, the areas differently contaminated, the amount of time spent in the concentration of the contaminants in air and water, the variability of the concentrations of contaminants in the air and water, etc. Because very little actual information is available, mathematical models are used to estimate exposures. As a result, conservative assumptions biased toward increasing the exposure estimate are used.

Risk Assessments are typically conservative. This is particularly true of those developed by agencies focused on public health and policy, such as ATSDR and EPA. “Unpacking” risk assessments to acknowledge and understand the level of conservatism in them is part of the Risk Characterization process; both EPA and ATSDR provide guidance on how this should be done. Recognizing,

---

<sup>13</sup> Neither EPA nor ATSDR develops risk values for the dermal route of exposure.

acknowledging, and discussing the impact of uncertainties, assumptions, and extrapolations in both the dose response analysis and exposure assessment must be undertaken in an unpacking and understanding of the results of the risk assessment.

## 8.2. What is Non-cancer Risk Assessment?

Non-cancer risk assessment is a threshold-based approach. Non-cancer risk values are derived from the results of human observations or animal toxicity studies. The dose response of the effects is examined to identify a shifting point between exposures that do not and those that do produce the effect. As practiced by EPA and by ATSDR, a dose point near this shifting point is identified, and then reduced to develop non-cancer risk values. Non-cancer risk values include ATSDR's Minimal Risk Level (MRL) values and EPA's oral Reference Dose (RfD) and inhalation Reference Concentration (RfC) values.

## 8.3. What are Non-Cancer Reference Values?

EPA's oral RfD and inhalation RfC values and ATSDR's MRL values are designed to serve the same purpose and are derived by the same methods. At times, EPA and ATSDR use different policies to make specific decisions<sup>14</sup> and what numerical values to apply for specific uncertainty factors. However, the purpose and methods remain the same across the two agencies.

EPA's oral RfD values and inhalation RfC values (but not MRL values) are used as the basis for environmental and standards.<sup>15</sup> Risk is avoided when exposures are kept at or below the identified levels, but the values have an ample margin of safety or health conservatism in them. This means that if exposures exceed their values, it does not necessarily mean that risk is anticipated. EPA develops RfD and RfC values for exposures up to a lifetime's duration within its Integrated Risk Information System (IRIS) program. These are defined:<sup>16</sup>

- **Reference Dose**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a No-Observed-Adverse-Effect-Level dose (NOAEL), Lowest-Observed-Effect-Level dose (LOAEL), or

---

<sup>14</sup> These decisions may include, for example, whether a data base deficiency is impactful at a level of 10 or 3; whether a 1 standard deviation difference represents a biologically meaningful difference or whether a one-quarter standard deviation difference is biologically meaningful; whether a lifetime-based risk value is applicable to a one-year human exposure; etc.

<sup>15</sup> "Standards" are typically legally enforceable values; MRL values are used to set guideline values, which are not legally enforceable.

<sup>16</sup> Integrated Risk Information System (IRIS) Glossary, at: [https://sor.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary](https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary)

benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. [Reference doses are g]enerally used in EPA's non-cancer health assessments.<sup>17</sup>

- **Chronic Reference Dose**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. [Chronic reference doses are g]enerally used in EPA's non-cancer health assessments.<sup>18</sup>

- **Subchronic Reference Dose**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a subchronic duration (up to 10% of average lifespan) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Subchronic reference doses are generally used in EPA's non-cancer health assessments.

- **Reference Concentration**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. [Reference concentrations are g]enerally used in EPA's non-cancer health assessments.<sup>19</sup>

- **Chronic Reference Concentration**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. [Chronic reference concentrations are g]enerally used in EPA's non-cancer health assessments.

- **Subchronic Reference Concentration**

Definition: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a subchronic duration (up to 10% of average lifespan) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. [Subchronic reference concentration are g]enerally used in EPA's non-cancer health assessments.

---

<sup>17</sup> Durations include acute, short-term, subchronic, and chronic and are defined individually in the IRIS glossary.

<sup>18</sup> Chronic RfDs are used as the quantitative basis for MCL values; MCL values generally equate to one-fifth the RfD.

<sup>19</sup> Durations include acute, short-term, subchronic, and chronic and are defined individually in this glossary.

Using a practice similar to EPA's, ATSDR defines MRL values:<sup>20</sup>

- An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. These substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. **It is important to note that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies.** (emphasis in original).

ATSDR's Public Health Assessment Guidance Manual (ATSDR, 2005) further explains the boundaries of MRL values:

- Represent estimates of the daily human exposure to a contaminant that, based on ATSDR evaluations, are not expected to cause non-cancer health effects during a specified exposure duration.
- Are set below levels that might cause adverse health effects in most people, including sensitive populations.
- Are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) exposure durations.
- Are available for oral and inhalation exposures.

#### 8.4. The PHA's Use of Reference Values

The PHA relied on EPA's RfD and RfC values as well as ATSDR MRL values (See ATSDR, 2017a, Tables 5a and 5b and Tables D-3 to D-10) as the basis for developing the values used in their risk assessment, specifically the Hazard Quotient and Hazard Index values.<sup>21</sup> The PHA failed to recognize, acknowledge, and discuss the impact of uncertainties, assumptions, and extrapolations from the above-defined reference values when unpacking its results.

First, ATSDR's definition of MRL values states that they are not intended to define clean up or action levels. However, the PHA disregarded this and used MRL values to develop Hazard Index values as support for conclusions drawn about health threats. In contradiction to the MRL's definition, the PHA states that "these reports identify what actions are appropriate to be undertaken by EPA, other responsible parties, or the research or education divisions of ATSDR." Thus, the use of MRL values to support conclusions about "actions to be taken" violates their intended application.

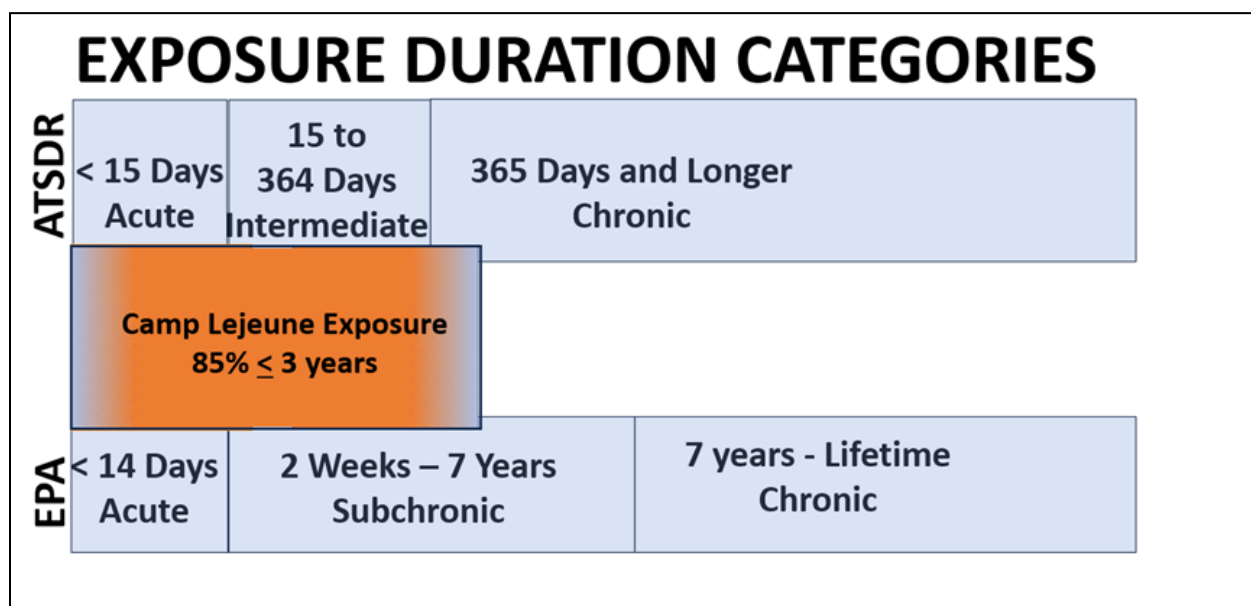
---

<sup>20</sup> Minimal Risk Levels (MRLs) – For Professionals, at: <https://www.atsdr.cdc.gov/mrls/index.html>

<sup>21</sup> A full discussion of Hazard Quotients and Hazard Index values can be found in Section 9 of this Report. Hazard Quotients express the ratio of an exposure to an acceptable level of exposure, such as an MRL or an EPA Reference dose. The Hazard Index is the sum of HQ values for individual chemicals in a mixture.

Second, ATSDR’s exposure duration categories do not align with those of EPA. ATSDR used EPA’s TCE chronic reference dose and chronic reference concentration values as ATSDR chronic oral MRL and chronic inhalation MRL values in the PHA. However, EPA defines “chronic” reference doses as applying to exposures between seven years and a lifetime. In effect, ATSDR has “renamed” these numerical risk values to “Minimal Risk Values” but stayed within the moniker of “chronic.” Because EPA defines “chronic” as a human duration only as short as seven years, the application of these values to durations shorter than seven years violates the application for which they were derived. This is problematic because EPA deems a chronic value to apply to exposure durations of seven years or longer, but ATSDR applies their chronic values to exposure durations as short as one year.

**FIGURE 3. Exposure Duration Categories**



**Figure 3. Exposure Duration Categories.** Using an EPA “chronic” duration risk value to evaluate exposures of less than seven years is contraindicated. The median residence time at Camp Lejeune was 18 months for Marine and Navy personnel. While 18 months is longer than 365 days, the application of a risk value developed for exposures of up to a lifetime raises serious questions. In some cases, EPA “chronic” values have been developed on the basis of “subchronic” experimental exposures, and ATSDR has adopted some EPA “chronic” values as “chronic” MRL values. Disconnects like this must be acknowledged to identify the implications of values like Hazard Quotients and Hazard Indices.

ATSDR treats exposures of only one year or longer as if they are “lifetime” (chronic) exposures, whereas EPA treats exposures greater than seven years (approximately 10% of a human lifetime) as “chronic.” Contradicting EPA guidance, the PHA has employed some EPA chronic duration values in deriving Hazard Quotient and Hazard Index values for an expected three-year duration. This assumes appreciable importance when ATSDR adopts EPA’s chronic duration reference values as ATSDR’s chronic duration MRL values.

Moreover, the PHA conservatively assumed a three-year exposure duration for Marines-in-training. ATSDR (2017b) reported that the median residence time at Camp Lejeune for Navy and Marine personnel was 18 months. In fact, only 15% of the Marines in training are estimated to have 3 years or more exposure. (ATSDR, 2017a). This duration is markedly shorter than the lifetime exposure duration covered by ATSDR and EPA “chronic” risk values. Instead, it aligns with EPA’s subchronic duration and minimally overlaps with ATSDR’s chronic duration. Similarly, ATSDR (2017a) also stated that 95% of Marines and their families resided on base for less than 4.8 years; ATSDR (2017b) reported median residence time of 18 months for Navy and Marine personnel. Thus, EPA chronic values are not appropriate to assess risk for an exposure of only 18 months; EPA subchronic values were more appropriate for inclusion in PHA.

The PHA failed to explain why ATSDR’s chronic duration values were deemed appropriate comparator values for most Camp Lejeune residents. As stated by EPA in its Risk Assessment Guidance for Superfund (EPA, 1989), a chronic EPA Reference Dose is defined as

“[a]n estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime.

**Chronic RfDs are specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to lifetime).”** (emphasis added).

The differences between the durations of exposure for experimental studies on which ATSDR reference values are developed versus the three-year assumed exposure at Camp Lejeune must be acknowledged. Such differences will introduce uncertainty into the use of ATSDR chronic risk values, especially chronic values from EPA, when they are used to evaluate the potential impact of Camp Lejeune exposures. Such differences highlight the contraindication for application of EPA chronic values and absolutely force a more detailed identification of the implications of such comparisons (e.g., Hazard Quotient and Hazard Index values, which are discussed in Section 9). Issues like these are topics that require further evaluation during an unpacking of the results of the screening assessment.

#### 8.4.1. Risk Values Developed for Longer Durations will Over-Estimate Risk from Shorter Exposures

For reference values to be accurate, it is imperative that human exposure durations be well-aligned with the durations of the experimental exposures. Otherwise, chronic reference values over-estimate the potential for health effects resulting from less-than-lifetime exposures.

One of the foundations of toxicology is the relationship between exposure and response. Exposure is measured in two dimensions: magnitude of exposure (dose) and duration of exposure (days, months, years). The traditional dose response relationship demonstrates that, for the same duration, several

things change as the dose increases: 1) the frequency of a response increases;<sup>22</sup> 2) the severity of the observed response increases; and 3) more and different types of responses will be observed. And, for the same dose, as the duration of exposure increases, the likelihood of a response also increases.

Another foundation of toxicology and risk assessment is the interdependence of dose and duration (Gaylor, 2000). This was codified as Haber's Law, where the response is the result of both the intensity of the exposure and the duration of the exposure. Together, the elements of intensity and duration define the exposure (the dose). The equation can be expressed as:

$$R = c \times t$$

Where R is the response, *c* is the exposure concentration,<sup>23</sup> and *t* is time or exposure duration.

From this we can see that if the exposure concentration or time goes up, the response will increase. And, if exposure concentration or time goes down, the response will go down. And so, if time is held constant while exposure concentration goes up, the response will go up.

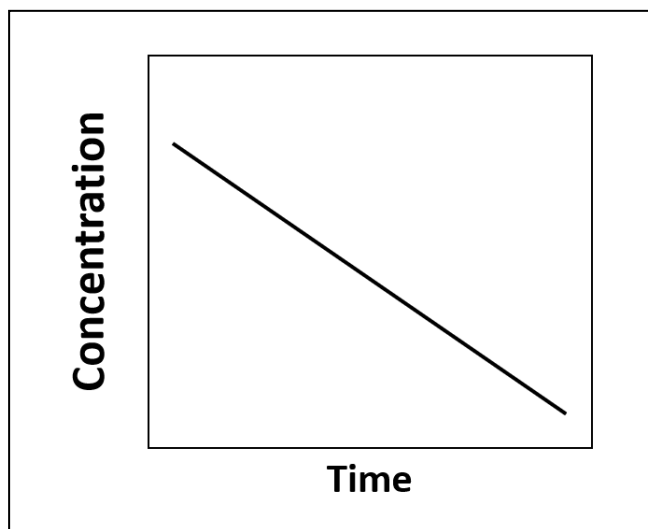
Figure 4 (below) demonstrates the inverse relationship between time and exposure concentration generally required to produce the same response. To maintain the same level of a response, if the concentration is increased it takes a shorter time to develop the response; and as the exposure time is prolonged, it takes a lower concentration to develop the response. Likewise, if the concentration is decreased it takes a longer time to develop the response; and as the exposure time is decreased it takes a higher concentration to develop the response.

---

<sup>22</sup> This occurs because sensitivity is not uniform in a population.

<sup>23</sup> Inhalation exposures are referred to as concentrations. Oral exposures are referred to as doses. In this example both inhalation concentration and oral dose have the same relationship with time – they are interchangeable terms here.

**Figure 4. The Influence of Concentration and Time on Response.**



**Figure 4. The influence of concentration and time on a constant level of response.** *This figure demonstrates the inverse relationship between exposure concentration and time required to produce the same level of a response.*

What this means is that risk values<sup>24</sup> developed on the basis of concentrations or doses continuing for longer exposure durations (like chronic risk values) will be lower than risk values developed on the basis of concentrations or doses continuing for shorter exposure durations (like subchronic or intermediate duration risk values), all other things being equal. Therefore, risk values developed for shorter durations will under-estimate risk from longer exposures, and risk values developed for longer (e.g., chronic) durations will over-estimate risk from shorter exposures. Accordingly, when performing a risk assessment, the risk value (e.g., the MRL value) used should be developed for a similar experimental duration (and, ideally, from the results of an experiment using a similar exposure duration) to increase confidence in the study results.

Where there is a reference value based on study durations that differ from the estimated human exposure, the risk assessment should justify such application. Because using a risk value based on findings from a longer duration study to evaluate the risks from a shorter-duration human exposure is something that cannot be quantified by an uncertainty factor,<sup>25</sup> it must be discussed in qualitative terms. It is not accurate to stop such a discussion at the name of the exposure duration bin (“Intermediate” or “Subchronic” or “Chronic”) to justify the application of the selected risk value. Some consideration should be given to evaluating the duration of exposure in the underlying toxicity study in addition to

---

<sup>24</sup> “Risk values” includes EPA Reference Dose and Reference Concentration, and ATSDR’s Minimal Risk Level values. “Reference Values” include only EPA Reference Dose and Reference Concentration values.

<sup>25</sup> A full discussion of uncertainty factors can be found in Section 8.10. Uncertainty factors are used to decrease the point of departure (POD) values from shorter experimental exposure durations to develop risk values for longer anticipated human exposures. However, there is no quantitative method for the reverse.

evaluating the degree of correspondence between the exposure duration in the scenario of interest and the exposure duration for which the risk value was developed.<sup>26</sup>

The PHA did not include such discussion. As explained in the preceding section, the PHA used chronic MRL and chronic reference values developed for exposures of up to a lifetime risk. This overestimated the risk for the multitude of individuals that experience shorter than chronic exposure. Due to the inverse relationship between duration and exposure concentration, the risk for shorter exposure durations was overestimated when using risk values developed for exposures of much longer than the average exposure of individuals at Camp Lejeune.

### 8.5. Non-Cancer Risk Values are Developed Through a Multi-Step Process

Once candidate critical effects have been identified, the process of quantifying candidate risk values and the “overall” non-cancer risk value begins. As shown in Figure 5, below and described in the following sections, the dose or concentration representing the Point of Departure is identified (e.g., 100 ppm) at this point in the process. The experimental exposure scenario (e.g., 6 hr/day, five days/week) is compared to the assumed continuous human exposure (i.e., 24 hr/day, seven days/week). If necessary, the Point of Departure is then mathematically adjusted to a continuous exposure level; this is duration-adjusted Point of Departure (POD<sub>adj</sub>).

The exposure scenario and the effect level of the Point of Departure are then evaluated. Data gaps exist when (1) a no-effect level cannot be identified from the experimental results, (2) the study does not capture the range of human variability, (3) the study was conducted in animals, (4) the study was conducted for a less than lifetime exposure, or (5) data are not available to address key types of toxicity studies (like reproductive and developmental studies). In these cases, EPA has established uncertainty factors to cover the data gaps, and these uncertainty factors are assigned numerical values, typically between 1 and 10. Once the uncertainty factor values are assigned, they are multiplied together to develop the composite uncertainty factor (CUF).

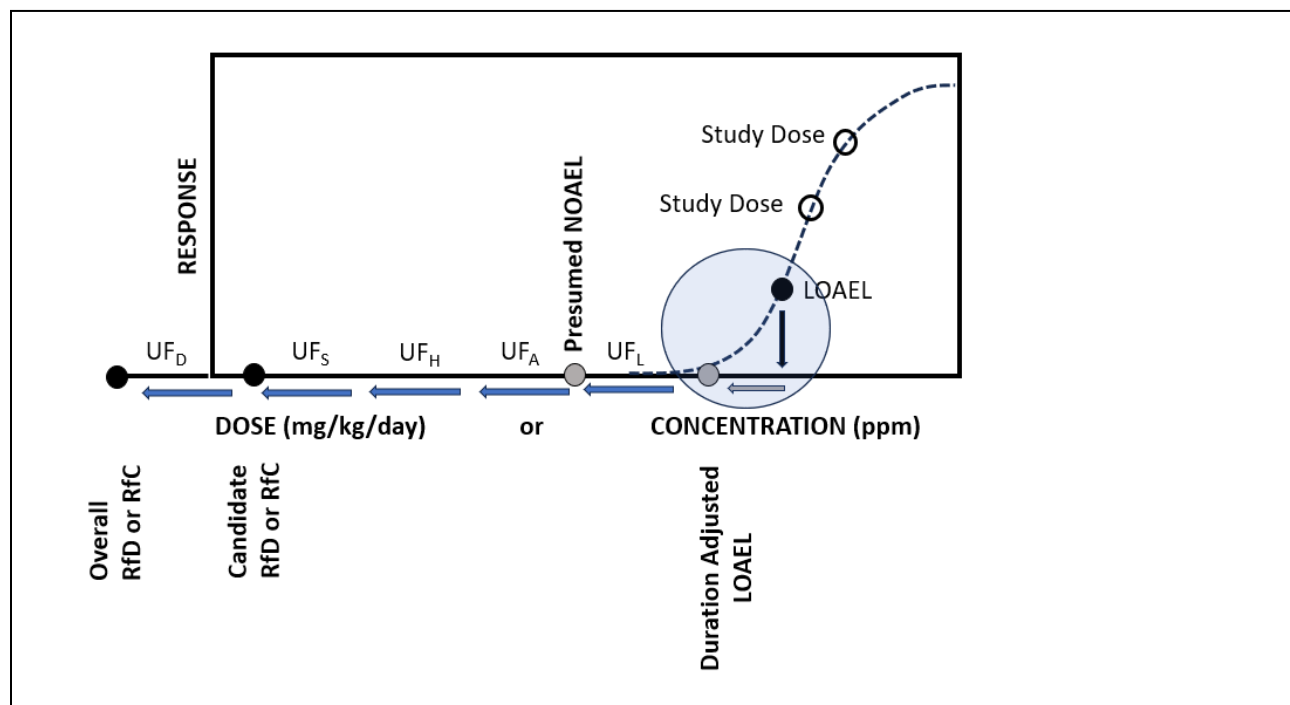
EPA and ATSDR calculate the non-cancer risk value by dividing the duration-adjusted Point of Departure by the CUF value, as shown below.

$$\text{Non-Cancer Risk Value} = \text{POD}_{\text{adj}} / \text{CUF}$$

---

<sup>26</sup> The exposure duration bins used by EPA and ATSDR are shown in Figure 3.

**Figure 5. Development of non-cancer reference values.**



**Figure 5. Development of non-cancer reference values.** The process shown is discussed in detail in the following text. The shaded circle indicates the process of duration adjustment. This process is used by ATSDR and by EPA to develop MRL values and Reference values, respectively.

### 8.5.1. The Method to Derive MRL values and EPA Reference Values Incorporates a Level of Conservatism Which is Then Imported into all Risk Assessments.

Risk values are not bright lines, and, as made clear elsewhere in this Report, reference values cannot be used to quantify risk at exposures that exceed reference values. Because many government exposure regulations are developed from reference values, driving down the reference values increases the health protectiveness in the reference values, imparting to them what EPA calls a “margin of safety.” Thus, reference doses are set at levels below which adverse effects can be expected. An exceedance of a reference dose does not necessarily mean that risk should be anticipated.

This section describes the three general steps involved in developing the inputs for this equation for non-cancer risk value development and describes some of the conservative aspects in each:

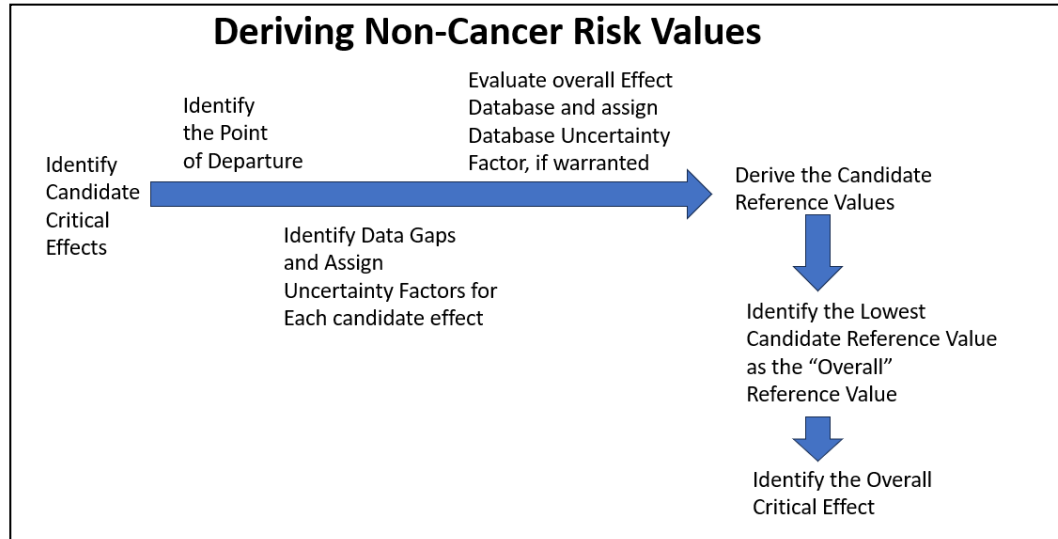
- identifying the candidate critical effect,
- identifying the point of departure,<sup>27</sup> and

<sup>27</sup> The Point of Departure is the dose used as the beginning of the low dose extrapolation to develop the risk value. This is discussed in detail in Section 8.9.

- choosing the values for the uncertainty factors.

ATSDR's and EPA's process to develop reference values is shown graphically in Figure 6.

**Figure 6. The Path to Develop a Reference Value.**



**Figure 6. The Path to Develop a Reference Value.** *Because different effects, and effects described in different studies may be assigned different uncertainty factor values, and because the point of departure values are divided by uncertainty factor values to develop risk values, not all effects (even those with the same point of departure) will result in the same risk value. EPA and ATSDR develop risk value to protect against "any harm", and so select the lowest possible risk value developed from the suite of effects studied.*

### 8.6. Identifying the Candidate Critical Effects

Candidate critical effects are identified in the Hazard Identification step of the Risk Assessment Paradigm. Here, the risk assessor is not yet concerned with doses, but identifies the effects that are associated with the chemical irrespective of the dose. But it is important to remember that not all candidate critical effects represent actual adverse effects. EPA<sup>28</sup> defines "adverse effect" as: "[a] biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge." So, when EPA chooses to develop a risk value on the basis of an effect that is not a direct measure of functionality, and/or is found at a level that has not been shown to reduce functionality, that represents a protective, health conservative decision.

<sup>28</sup> <https://www.epa.gov/iris-glossary>

Chemicals can produce several effects, each with its own dose response relationship. These effects may be described in different studies<sup>29</sup> and occur at different doses. Some effects are more sensitive than others. The several effects produced are called “candidate critical effects”, and one of these will later be identified as the critical effect. The critical effect is the most sensitive of the effects observed in studies of the chemical – this means that it is the effect that produces the lowest risk value. The critical effect cannot be identified until all candidate critical effects have been taken through the process to develop risk values.<sup>30</sup> Developing a risk value that protects against the critical effect will also protect against all the other candidate critical effects.

Just because an effect can be measured biochemically does not mean that it is adverse. Different effects occur along the Toxicity Pathway and may occur in a progression that moves along as the dose increases. The cascade of individual events that may end in an actual adverse effect may have many points where measurements can be made. Basing a risk value on a measured effect that is not adverse results in a more protective risk value than basing a risk value on an effect that is actually adverse. For these reasons, and as advocated-for by EPA (2014, 2022a), the relationship of the measured effect to the actual health endpoint should be known. Such knowledge aids in the interpretation of risk from exposures that may exceed the reference value developed on the basis of a given effect. The assumption that all measured events are adverse is a conservative, health protective assumption which contributes to the “margin of safety” inherent in risk values.

### 8.7. The Dose Response Analysis

Once the candidate critical effects are identified, they are evaluated as the first stage of the Dose Response Analysis step of the Risk Assessment Paradigm. This stage identifies the Point of Departure. To do so, study data that characterize the effect at the different study doses are laid out according to increasing dose. Some lower doses may not show the effect, while some higher doses might. In this format, the relation between increasing dose and the level or severity of the effect is displayed. Statistical modeling of the entire set of dose response data might be possible. EPA has created the Benchmark Dose (BMD) modeling software<sup>31</sup> to model the dose response and both EPA and ATSDR reply on this statistical modeling approach. If the entire set of dose response data cannot be modeled as a set, then the risk assessor will have to rely on the default approach of statistical evaluation of the individual doses. Whether through BMD modeling or the default approach, this stage identifies the Point of Departure, which is the only aspect of the dose response relationship that is carried forward into developing the risk value.

---

<sup>29</sup> The different studies may be conducted for different exposure durations and may have different uncertainty factors. This is discussed more fully in Section 8.9.

<sup>30</sup> The candidate risk values developed from candidate critical effects can be used as Target Organ Toxicity Dose values.

<sup>31</sup> BMD modeling is also the preferred method for cancer risk assessment.

## 8.8. Determining the POD Value Underestimates the True Threshold for the Response.

To determine the Point of Departure by BMD modeling, the risk assessor determines what response level<sup>32</sup> to have the BMD software evaluate. It should be noted here that there is not a response level that is acknowledged to be adverse. The software identifies the dose<sup>33</sup> that results in the response level, and also the dose that is at the 95% lower confidence bound of doses identified. The risk assessor picks the lowest lower confidence bound dose to use as the Point of Departure dose for deriving the risk value for that effect. And, so, the POD value might be a dose that has a 95% chance of being too low to result in the arbitrary response level, for an effect that may not be adverse. This represents an appreciable level of conservatism, and applies to the Point of Departure identification only.

If statistical modeling is not possible, then the risk assessor falls back to the “default” approach to identify the Point of Departure as one of the study doses (see Figure 7 below). In this approach, the statistical significance of each dose is determined, and the highest dose that does not produce a statistically significant difference from the untreated group is identified as the No-Observed-Adverse-Effect-Level (NOAEL). The lowest dose that produces a statistically significant difference from control is identified as the Lowest-Observable-Adverse-Effect-Level (LOAEL). If a NOAEL is identified, then it serves as the Point of Departure. If the lowest dose tested is the LOAEL, then the LOAEL is identified as the Point of Departure.<sup>34</sup> As shown in Figure 7, if a NOAEL is identified as the Point of Departure, then the true threshold is underestimated; the true threshold will be a dose above the NOAEL and below the LOAEL.

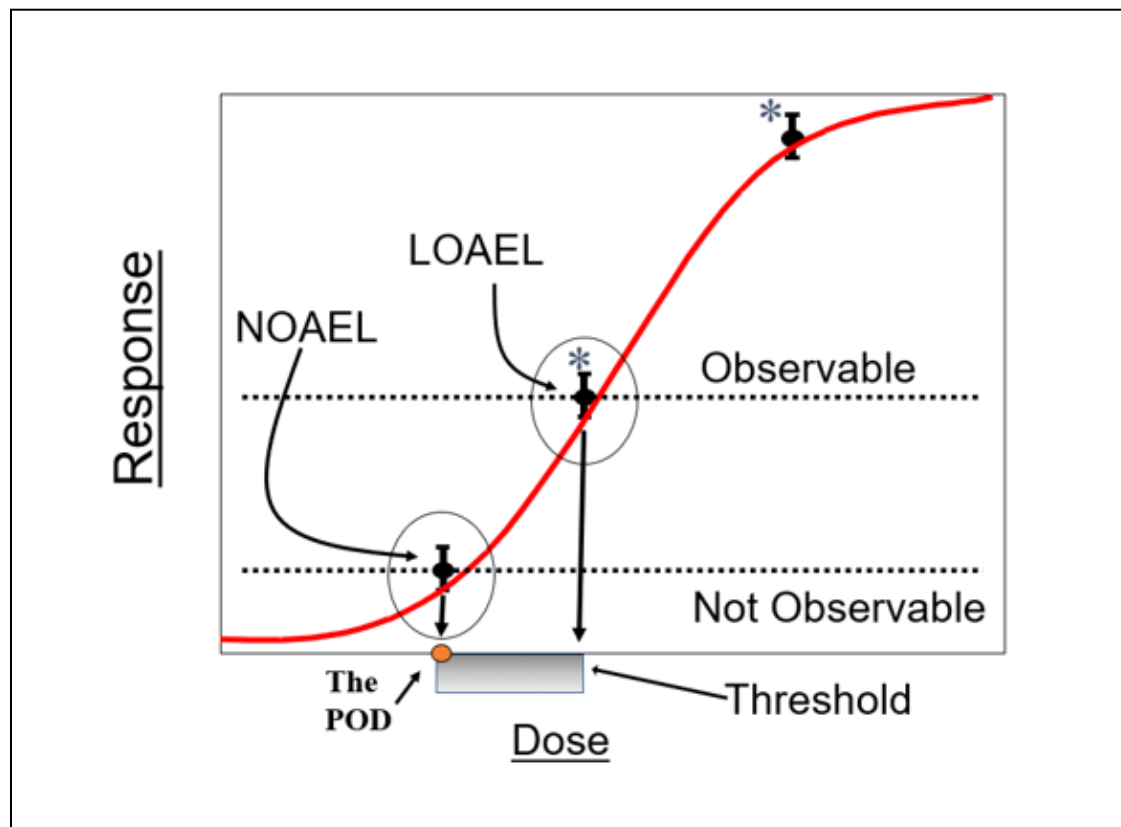
---

<sup>32</sup> The response level is the fraction of the group responding, and typical values are 1%, 5% and 10%.

<sup>33</sup> The dose identified will not be one of the doses studied; it is statistically determined and maybe any dose.

<sup>34</sup> <https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-3>

**FIGURE 7. The Default Method to Identify a Point of Departure**



**Figure 7. The Default Method to Identify a Point of Departure.** *This figure depicts hypothetical results of a toxicity study in which the top two doses produced a statistically significant increase in the effect. Because experiments generally test relatively few doses among the infinite number possible, the true threshold for the effect (the gray rectangle) will be higher than the NOAEL. Thus, identifying the NOAEL as the POD represents a health conservative approach, as the true threshold will be higher than the NOAEL dose. This contributes to the margin of safety embodied in derived risk values (Lipscomb, 2021).*

Next, EPA defines<sup>35</sup> the point of departure as the dose response point (an inhalation concentration or oral ingestion dose) that marks the beginning of a low-dose extrapolation for a given effect. After identifying the POD, the information describing the relationship between other doses and the response are lost. No information about the frequency or severity of the response at doses below or above the point of departure appear in the risk assessment process beyond the process of identifying the point of departure.

<sup>35</sup>[https://sor.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do;jsessionid=GSTImKnWQdLYIWDt\\_GcD\\_R2JKZ\\_MhDsw4cj7CjcEOelhaX6gTvU!1465299113?details=&vocabName=IRIS%20Glossary&filterTerm=point%20of%20departure&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=point%20of%20departure&filterMatchCriteria=Contains](https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do;jsessionid=GSTImKnWQdLYIWDt_GcD_R2JKZ_MhDsw4cj7CjcEOelhaX6gTvU!1465299113?details=&vocabName=IRIS%20Glossary&filterTerm=point%20of%20departure&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=point%20of%20departure&filterMatchCriteria=Contains)

Again, the POD may be identified on the basis of a statistically significant change in the effect, without confirmation that the magnitude of change in the effect represents a biologically meaningful change, and without consideration of whether the effect itself is biologically relevant. In other words, the POD may show an effect on paper, but it may not represent a biologically relevant event.

### 8.9. The Point of Departure Dose is Identified, then Reduced.

Three exposure durations are important in risk assessment:

- the duration of the experimental observations upon which risk values are based,
- the human exposure for which the risk value is developed, and
- the actual human exposure to which the risk value is applied.

When developing a risk value, the first two durations are addressed. When the POD is not derived from a continuous experimental exposure, the POD must be adjusted. The exposure duration is an important aspect here. The effects of an intermittent experimental exposure<sup>36</sup> are extrapolated to estimate the effects from a continuous exposure.<sup>37</sup> This begins with a Duration Adjustment of the POD which adjusts the POD value from the typical intermittent experimental exposure to a continuous exposure which humans are assumed to experience. Recalling the “ $c \times t$ ” relationship (described in Section 8.4.1), it is assumed that the effect that is observed from a short-duration high-concentration exposure will also be observed from a longer-duration, lower-concentration exposure. A two-stage Duration Adjustment may be necessary. The first adjustment is to continuous, daily exposures. To illustrate, if the Point of Departure is 100 ppm for an exposure of 6 hours/day, the daily duration adjustment would be:

$$100 \text{ ppm} \times (6\text{hr} / 24\text{hr}) = 25 \text{ ppm.}$$

And, if the exposure was only for five days a week, then a second duration adjustment is necessary to account for the number of days per week that the experimental exposure occurred, shown below:

$$25 \text{ ppm} \times (5\text{days} / 7\text{days}) = 18 \text{ ppm.}$$

This magnitude of adjustment is typical for animal experimental inhalation experiments – where an actual POD concentration of 100 ppm is reduced to a duration adjusted POD of 18 ppm.

There are concerns for effects that are identified from exposures to high doses or concentrations for short periods of time, which may not be seen with exposures to lower concentrations for longer durations of time. Intermittent type exposures like those from an experimental inhalation duration of 6 hours per day or an “all-at-once” daily oral dose delivered by stomach tube<sup>38</sup> can cause effects not otherwise seen. When tissues are exposed for short durations to high tissue concentrations, the tissue

---

<sup>36</sup> Typical animal experiments do not involve a continuous exposure. Inhalation exposures are often for a limited number of hours, for five work days per week. Oral exposures are often daily doses given five work days per week.

<sup>37</sup> For risk assessment purposes, humans are assumed to be exposed 24 hours a day, seven days a week.

<sup>38</sup> Also known as a bolus dose.

response may not be the same as if the tissue had been exposed to a lower concentration over a longer duration. The inhalation example above demonstrates an approximate five-fold difference between the actual concentration of 100 ppm and the duration-adjusted concentration of 18 ppm. These higher concentrations, even when encountered for short durations, can for some chemicals, and for some effects, induce changes or cause effects not seen at lower concentrations.

Because experimental exposures are often for shorter durations but to higher doses or concentrations, assuming that the actual experimental exposure and the duration-adjusted exposure result in the same effect and the same level of response introduces another level of health conservatism and adds to the margin of safety embodied in derived risk values. Some concerning aspects of oral gavage dosing, including when used in studies of TCE, have been raised (Conolly et al., 2023; Lilly et al., 1996; Stermer et al., 2019).

#### 8.9.1. POD Values do not Capture Dose Response Data, and so Prevent the Ability of Risk Values to Quantify Increased Risk.

The slope of the dose response relationship describes the increase in the effect (if there is one) relative to the dose, and describing this is an important part of the risk characterization process.

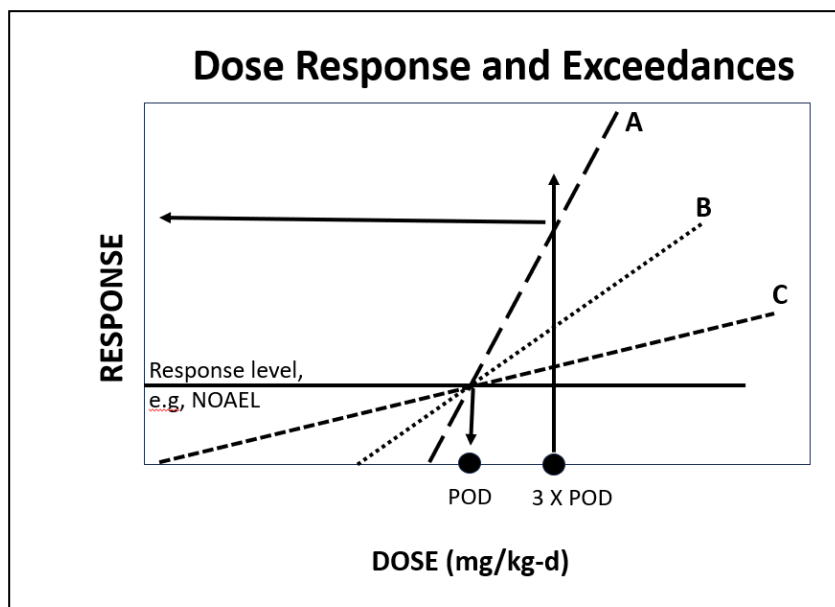
Of all the study doses used, only the POD is used in developing risk values. Although the whole set of dose response data shows whether or how much the effect increases at doses higher than the POD, the whole data set is not used. While the POD is determined from the dose response data, sometimes by statistical modeling of the whole set of dose response data, risk assessment practice<sup>39</sup> does not use information from the whole set of dose

response data. Risk assessment practice uses only the POD value. When the only data point from the whole set of dose response data that is used is the POD value, then there is no way to estimate the extent that the effect might increase at doses higher than the POD. This is shown in Figure 8.

---

<sup>39</sup> This applies to both non-cancer and cancer risk assessment.

**FIGURE 8. Dose Response and Exceedances.**



**FIGURE 8. Dose response and Exceedances.** *This figure demonstrates why only knowing the POD restricts what can be understood about the dose response relationship – with a special emphasis on the potential responses from doses higher than the POD. This directly impacts the interpretation of risk from exposures that exceed reference values. Here, three possible dose response relationships (A, B, C) are depicted for the same effect, and each has the same POD value but different slopes.*

Knowing only the POD value (or only the reference dose, reference concentration, or MRL) prevents an interpretation of the risk of exposures that exceed that known value. Using the example of Figure 8 above, dose response relationship A has the steepest slope. For dose response relationship A, a dose that is three-fold above the POD would be expected to result in a more severe response than the same three-fold exceedance if the dose response relationship has a gentler slope, such as that for B or C. This is because dose response relationships B and C have shallower slopes. But, without knowing the full dose response relationship, how much the effect would be increased with an increased dose is not something we can determine.

This failure to capture the full dose response data is a primary reason why it is impossible to use non-cancer POD-based risk values to quantify risk when exposures exceed guidance values.

#### 8.10. Uncertainty Factors Cover Data Gaps and Reduce the Point of Departure

After the POD is duration-adjusted, the next step is to identify data gaps between the experimental exposure and the effect severity, and then account for them by applying uncertainty factors. There are several potential data gaps represent that may apply when extrapolating a POD value to develop a risk value. Uncertainty factors have numerical values assigned to them. When there are data for the chemical to cover a potential data gap, those data are used and the value for that uncertainty factor is set to a value of 1. But, when that data gap is real (when there are not data to cover that particular area), a value higher than 1 is applied, typically 10.

EPA and ATSDR aim to protect even the most sensitive humans against chemical harm and assume a life-long exposure. However, data gaps exist when the underlying toxicity study does not represent the most sensitive humans exposed for a lifetime without being adversely affected. Therefore, when basing the

risk value on the results of a study in animals, four data gaps are possible, and the uncertainty factors (UF) associated with them have been identified.

- UF A (Animal) is applied when the study is conducted in animals; it has a default value of 10.
- UF H (Human) is applied when the study is from humans, but not the most sensitive humans; it has a default value of 10.
- UF L (LOAEL) is applied when the POD is the lowest observed adverse effect level, not a no observed adverse effect level; it has a default value of 10.
- UF S (Subchronic) is applied when the study was conducted for less than a lifetime; it has a default value of 10.

Whether these uncertainty factors apply and what their values are depends on the underlying study being considered.

UF A and UF H can be reduced or increased on the basis of data specific to the chemical following US and International guidance (EPA, 1994, 2011c, 2014b; IPCS, 2005). Chemical specific procedures exist for both animal-to-human extrapolation (UF A) and human variability (UF H), and default (not specific to any chemical) procedures based on body weight scaling (not body surface area) for oral exposures (EPA, 2011c) and based on blood solubility for inhalation exposures (EPA, 1994) are also available.

A species extrapolation of inhaled TCE concentrations has been reported by Plaintiffs' Expert Dr. Cannon, relying on Adamson et al. (2023). Adamson et al. (2023) used an incorrect method to extrapolate an inhalation exposure concentration of 50 ppm in rats and 100 ppm in mice to a human equivalent concentration of 8 ppm. Dr. Cannon failed to recognize this error. EPA (1994) established proper methodology for the extrapolation of inhalation concentrations from animals to humans based on the solubility of a chemical in blood of animals and humans. Using EPA's guided method and data supplied in EPA risk assessment for TCE (EPA, 2011a), the correct human equivalent concentration would be 50 ppm from the rat concentration of 50 ppm and 100 ppm from the mouse concentration of 100 ppm. EPA guides a conservative extrapolation by this method, meaning that the blood solubility data indicate that the human equivalent concentration would be higher, not equal to or lower than the concentrations inhaled by rats or mice.

Data from actual chemical toxicity studies have provided a basis to evaluate the health protectiveness of the default values of 10 for UF L and for UF S. Dourson and Stara (1983), Kadry et al., (1995), and Lewis et al. (1990) demonstrated that LOAEL to NOAEL ratios were less than 6, indicating a near two-fold level of health conservatism in the default value of 10 for UF L. Beck et al. (1993), Dourson and Stara (1983), and Kadry et al. (1995) reported that the most frequently determined ratios of subchronic to chronic POD values were 2.5 or less. This would indicate an approximate 4-fold level of health conservatism in the default value of 10 for UF S. What this means is that together a level of conservatism for these two factors approximates 8-fold. Considering information like this adds a quantitative perspective when evaluating estimates of risk based on a comparison of exposures to risk values.

There is an additional uncertainty factor that does not apply to the underlying study used to identify the POD, but to the broader body of information available for the chemical; EPA calls this the database uncertainty factor (UF D) and ATSDR calls it the Modifying Factor. It applies when the overall database for the chemical lacks studies for other areas that are thought to be important to that chemical. This factor can have a value from 1 to 10 depending on the amount of missing information. It is important to

understand that this factor does not apply to the studied effect, and this is made clear in ATSDR's definition of the Reference Dose,<sup>40</sup> in which the modifying factor is presented as a "separate" factor from the uncertainty factors.

**Reference Dose (RfD)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

As for the uncertainty factors, considering whether the database uncertainty factor applies to the effect evaluated or to the lack of other information is important. For example, in the Toxicological Profile for Tetrachloroethylene, ATSDR (2019b) developed a chronic inhalation MRL for PCE that included a value of 3 for the modifying factor, which was necessary because of the lack of data to address the possibility of low dose immune effects. Based on an unidentified Target Organ Toxicity Dose (TTD) value<sup>41</sup> for liver effects, the PHA develops an HQ value of 3.6 for potential liver effects in children exposed via inhalation to PCE at Tarawa Terrace (ATSDR, 2017a, p 29). Because the source of the TTD value is not identified in the PHA, further evaluation of the basis for the liver TTD value, including the point of departure and uncertainty factors used cannot be undertaken.

Using an inhalation TTD value for liver effects that includes a modifying factor value of 3 that is not related to liver effects imparts a level of conservatism that is unwarranted when considering the risk of liver effects. Considering the basis for the modifying factor when characterizing the risks that may be associated with organ-specific HQ values adds quantitative perspective. In this instance, if the modifying factor value of 3 was inappropriately used to develop the TTD for liver effects, and then increase the HQ for PCE-associated liver effects in children, the TTD for liver effects should be increased by a factor of 3. This would result in a reduction of the HQ value by a factor of 3, from a value of 3.6 to 1.2 – which rounds to 1. Discussions of the numerical values of uncertainty factor and applicability of the modifying factor values would be part of a Risk Characterization discussion, but are not included in the PHA.

---

<sup>40</sup> Definition taken from ATSDR's Toxicological Profile for PCE, ATSDR (2019b). This document indicates that the modifying factor of 3 is assigned based on what ATSDR considered was a lack of data describing the low dose immune effects possible for PCE.

<sup>41</sup> TTD values are discussed in more detail in Section 10.7.5. Tables 5a and 5b in the PHA (ATSDR, 2017a) present point of departure values and combined uncertainty values for the effects which are the critical effects for chemicals of interest. However, liver is not the critical effect for PCE, and these tables do not identify the point of departure or the uncertainty factors used to develop the TTD for liver effects of PCE. This criticism extends to other effects that do not represent the critical effect for other chemicals of interest.

## 8.11. What is Cancer Risk Assessment?

As part of risk assessments, risk assessors may look specifically to potential cancer risk. Like non-cancer risk assessment, cancer risk assessment begins by estimating a conservative risk value (a potency factor). It differs from non-cancer risk assessment in that cancer risk assessment then multiplies an estimated exposure by the potency factor to develop an upper bound probability of cancer. As for non-cancer risk, EPA and ATSDR have advised that cancer risk estimates have no prognostic value, and are conservative over-estimates of true risk. Recognizing the impact of conservatism applied at multiple steps in the cancer risk assessment process, EPA (2005) writes, “[o]verly conservative assumptions, when combined, can lead to unrealistic estimates of risk.” ATSDR’s PHA (ATSDR, 2017a) develops conservative estimates cancer risk for Camp Lejeune residents and individuals. In discussing their estimated cancer risk, ATSDR (2017a) writes, “[b]ecause of the uncertainties and conservative assumptions inherent in deriving the cancer slope factors, this is only an estimate of risk; the true risk is unknown and might be as low as zero (ATSDR 2005).” In other words, the PHA, itself, acknowledges that its cancer risk assessment is not a true measure of risk. Thus, reliance on the upper bound estimates of theoretical cancer risk presented by ATSDR (2017a) is of no prognostic value in actual risk (or causation) estimation.

Cancer risk assessment is generally based on a non-threshold approach and is calculated by multiplying the exposure dose by EPA’s cancer potency factor<sup>42</sup> to estimate risk as a probability. In the absence of data to the contrary, EPA assumes that the carcinogenic mode of action may include a genetic basis and so applies a linear, non-threshold model which in essence assumes that no exposure is without risk. For Superfund sites (like MCB Camp Lejeune) EPA considers that risk between one in ten thousand (1 in 10,000;  $10^{-4}$ ); and one in one million (1 in 1,000,000;  $10^{-6}$ ) represents an acceptable range of risk,<sup>43</sup> as indicated in Figures 9 and 10 of the PHA.

For mixtures of chemicals where an exposure estimate and a slope factor are available for each chemical, the upper bound estimate of risk is typically calculated for each chemical and the risk estimates are summed for the mixture. An important consideration here is the cancer Weight of Evidence classification for each chemical. This describes the likelihood that the chemical is carcinogenic to humans, with classification descriptors like “Carcinogenic to Humans”, “Likely to be carcinogenic to humans”, etc. These classifications depend on the strength of evidence from humans and from animals, and the difference distinguishes the two classifications mentioned above. When combining the estimated upper bound cancer risks from chemicals, it is important to consider their cancer descriptors to aid a more complete understanding of the implications of numeric estimates of cancer risk. For the chemicals of interest at Camp Lejeune, vinyl chloride (using older nomenclature current in 2000) is described as being a known human carcinogen by the inhalation route, extended to the oral route but

---

<sup>42</sup> ATSDR does not develop cancer potency factors.

<sup>43</sup> See Office of Solid Waste and Emergency Response OSWER DIRECTIVE 9355.0-30; and definitions of Acceptable Risk and Acceptable Exposure Levels at <https://semspub.epa.gov/work/HQ/100003059.pdf> and <https://semspub.epa.gov/work/11/176250.pdf>

without confirmation by positive evidence in orally-exposed humans. Benzene was characterized by EPA in 2003 as being a known carcinogen by all routes of exposure. PCE was characterized in 2012 as “Likely to be carcinogenic to humans”, and TCE was characterized in 2011 as “carcinogenic to humans.”

Cancer risk assessment inherently includes a level of conservativeness including in the mode of action, exposure assumptions, duration, potency factors, and Cancer Risk Evaluation Guideline (CREG) values. Each are discussed below.

#### 8.11.1. Mode of Action-Based Conservatism in Cancer Risk Assessment

Unless EPA determines that the cancer mode of action does not involve a DNA interaction and if EPA determines that a DNA interaction is not potentially plausible, EPA applies the linear low dose extrapolation to estimate cancer risk. What that means is when the cancer mode of action is unknown and when data have not shown that a DNA interaction is not possible, EPA applies the conservative approach to estimate cancer risk. This approach justifies the application of the linear low dose extrapolation method to estimate an upper bound cancer risk for Camp Lejeune chemicals.

Application of the linear, no-threshold risk model to chemicals which do not cause cancer through direct DNA interaction represents a health-protective, conservative approach. In those cases, doing so over-estimates cancer risk, especially at low doses.

Another aspect of mode of action is similarity of mode of action. EPA (2023) indicates that cancer risks are usually added together when the chemicals are “similar in terms of carcinogenicity.” However, for TCE, EPA (2011a) has erred on the side of conservatism by first scaling the potency of TCE for Non-Hodgkins lymphoma and liver/biliary cancer (for which the mode of action is unknown), to the potency of TCE for kidney cancer, for which EPA determined the data to be supportive of a DNA interaction. However, whether these represented effects that were similar in terms of carcinogenicity was not substantiated. Further, for cancer risk assessments conducted (e.g., ATSDR’s PHA, Rosenfeld et al., 2024), whether the tumors produced by the different chemicals in the mixture were similar in terms of carcinogenicity was not addressed. The assumption of toxicologic similarity that serves as the basis for summing cancer risks across cancer types and chemicals represents a conservative assumption that should be acknowledged.

EPA (EPA, 2011a) reviewed the available human studies and findings reported by the National Academies of Science and has concluded, “[i]nvestigations of nephrotoxicity in human populations show that workers highly exposed to TCE exhibit evidence of damage to the proximal tubule (NRC, 2006),” and “[h]uman studies have shown increased levels of proximal tubule damage in workers exposed to high levels of TCE (NRC, 2006).” Furthermore, ATSDR (2019a) concluded, “[n]o clear evidence of kidney effects has been reported in studies examining the association of long-term exposure to trichloroethylene in drinking water and adverse health effects.” EPA (2011a) also considered the dose response of renal cell carcinoma in occupationally exposed humans, writing, “[a] major uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures.” This seems to mirror a similar concern expressed by the authors of the underlying study: “[t]his study suggests an association between exposures to high levels of TCE and increased risk of RCC [renal cell carcinoma]” (Charbotel et al., 2006).

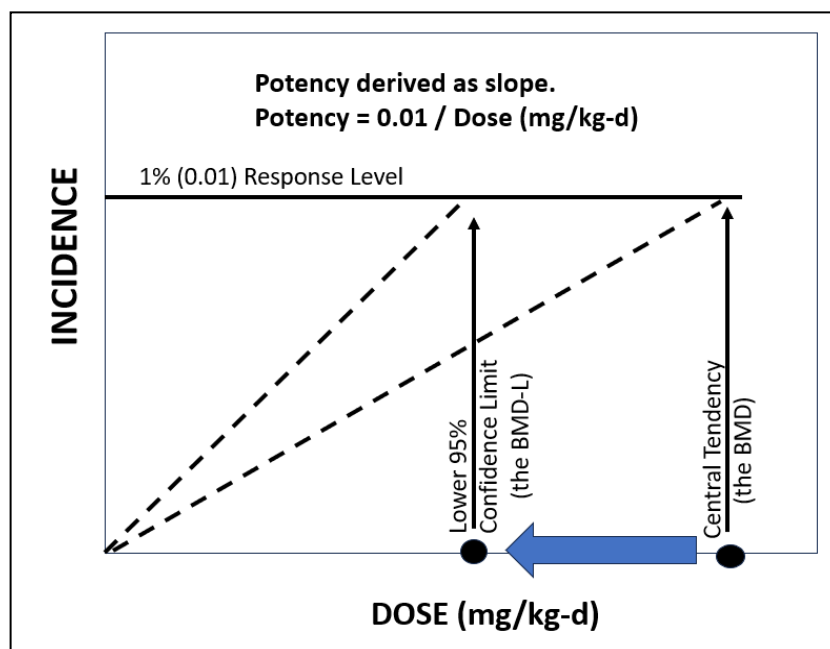
### 8.11.2. Exposure Assumption- Associated Conservatism in Cancer Risk Assessment

ATSDR has made it clear in the PHA (ATSDR, 2017a, p.80) that “[t]he actual parameters of environmental exposures must be considered carefully in evaluating the assumptions and variables relating to both toxicity and exposure (ATSDR 1993).” However, some assumptions seem quite unlikely. One such assumption is that the maximum estimated airborne concentration from indoor water use (e.g., showering) is sustained without decline as might be expected from ventilation in the structure. Such assumptions likely over-estimate exposure and should be discussed when unpacking the risk assessment.

### 8.11.3. Point of Departure-Based Conservatism in Cancer Risk Methods

When applying the linear low dose extrapolation method, the POD is preferably determined via benchmark dose modeling, with the same issues applying as identified for the BMD application in non-cancer risk assessment. Likewise, the POD value is determined as a benchmark response level, typically a 1% response level. Further, the lower 5% confidence bound on dose, not the central tendency (50% level) measure of dose, is used. What this means is that the cancer potency factor is derived from a dose anticipated to result in cancer in 1% of the exposed individuals, and at a dose that has a ten-fold elevated chance of under-predicting the median dose associated with the 1% cancer response. This is illustrated in Figure 9.

**FIGURE 9. Quantifying the Cancer Point of Departure**



**FIGURE 9. Quantifying the Cancer Point of Departure.** This Figure demonstrates the quantification of cancer risk using the linear low dose extrapolation method. Two estimates of the point of departure are typically calculated: the central tendency measure, for which the mathematical model is the most confident, and the lower 5% confidence bound dose, which is derived to account for mathematical uncertainty.

For the chemicals of interest at Camp Lejeune, estimation of cancer risk<sup>44</sup> is done by using a slope factor to complete the linear low dose extrapolation, assuming that there is no threshold – no dose resulting a zero risk.<sup>45</sup> Under the linear dose model, a straight line is drawn from the origin (0 dose, 0 response) to the cancer POD value (shown in Figure 9). The slope of this line (rise over run) is the slope factor, in units of risk per unit of dose (e.g., mg/kg/day). Accordingly, the slope factors for the chemicals of interest for Camp Lejeune also incorporate this level of conservatism and, thus, it enters the PHA.

#### 8.11.4. Duration-Associated Conservatism in Cancer Risk Assessment

Cancer risk quantitative methods involving the linear low dose extrapolation method are based on an understanding of cancer risk from radiation. In toxicology, it is accepted that it is the accumulated radiation dose that drives cancer, whether that dose is encountered in short durations (e.g., over exposures from nuclear accidents of past warfare associated exposures), or over a lifetime. This is known as the concept of cumulated or cumulative dose. Noting the similar DNA interaction related to radiation and chemicals, this cumulated dose concept became conceptualized in the linear low dose extrapolation method, where it is assumed that there is no dose without some risk. And the higher the cumulated dose, the higher the risk.

But, in reality, this may not be true. Chemicals differ from radiation in that the radiation-induced DNA active mode of action is the same at high doses and at low doses. Biologic processes that might reduce the chance of radiation interacting with DNA are not present. This contrasts with the availability and activity of biologic processes that can reduce or prevent the likelihood that a chemical may interact with DNA. Some of these processes include the elimination of the chemical via exhalation in the lungs, elimination in the urine and/or feces, metabolic processes that chemically change the chemical, and other processes like the temporal sequestering of a chemical through binding to non-affected proteins like those in the bloodstream. In addition, radiation can interact with virtually any number of DNA molecules as it passes through the tissues, whereas a chemical can only interact with one molecule of DNA per molecule of chemicals. Once a chemical molecule has interacted with DNA, it is “done.”

In this regard, cancer risk for chemicals encourages a temporal compression of dose, which assumes that the cancer risk is the same for (e.g.) an exposure to 1 ppm for 70 years as for an exposure to 10 ppm for 7 years or to 100 ppm for 0.7 years. This ignores the acknowledgement that higher doses of chemicals as used in animal studies can lead to the saturation of some biologic processes, leading to different types and different levels of internal exposures. It further ignores the concept of dose-dependent modes of action,<sup>46</sup> which generally represents one of the dose response principles: as the dose increases more and

---

<sup>44</sup> This is not “true risk.” Because of uncertainty and conservatism in cancer potency values, ATSDR acknowledged that “true risk may be as low as zero” when computed by this method. (ATSDR, 2017a).

<sup>45</sup> This method of calculation is based on knowledge of the mode of action involving a direct interaction with DNA. If the mode of action is not known, EPA applies the linear low-dose extrapolation as a health-protective default.

<sup>46</sup> See Slikker et al., *Toxicological and Applied Pharmacology*, 2004.

different types of effects are seen.<sup>47</sup> This concept is clearly demonstrated in non-cancer risk assessment via the development of the Target Organ Toxicity dose approach to mixtures risk assessment. Here, effects that are less sensitive than the critical effect (i.e., effects that only arise at doses higher than the dose associated with the most sensitive effect) are also quantified. Clearly, an exposure concentration of 100 ppm results in a higher probability that at least one atom of chemical will persist and interact with DNA than results from an exposure of 1 ppm. For chemicals lacking data supporting a DNA interaction as a part of their cancer mode of action, the application of these principles to assess cancer risk results in an even higher level of conservatism. Time-normalizing exposures to lifetime-averaged exposures ignores the possibility that there may be dose (concentration) dependent shifts in the likelihood and the extent that chemicals interact with biological molecules.

But time is also important in the context of exposure duration. Rat and mouse toxicity tests for lifetime exposures usually use a two-year exposure duration. Most cancer slope factor values based on animal studies are from two-year (104 week) studies. The value of cancer studies of a shorter exposure period is established by EPA (2012b) in its evaluation of a study by NCI (1977). Here, NCI exposed mice for 78 weeks and allowed a 32-week no-exposure follow-up period before the animals were sacrificed and tested for cancer. EPA concluded that the results of a study with an exposure period of roughly 75% of a lifetime would fail to produce cancer rates observed if the exposure was a full two years. EPA (2012b) wrote, “[f]irst, dosing lasted 78 weeks [followed by a 32-week no-exposure period prior to sacrifice] rather than 104 weeks as in the inhalation studies. Thus, in making direct comparisons, it might be expected that the observed tumor incidence in the NCI (1977) study would underestimate the incidence associated with 104 weeks of exposure.” So, what this means is within rodents, cancer developing from an exposure of approximately 75% of a lifetime would be overestimated using cancer data from a lifetime exposure. This stands in stark contrast to an extrapolation of cancer estimates from rodents to humans and extended to cover an exposure duration of approximately 4% of a lifetime (3 years / 70 years = 0.043). But this overestimation is what is done in the PHA.

When it is known that a chemical produces cancer by directly interacting with DNA, EPA invokes a linear low dose extrapolation method based on the  $c \times t$  relationship,<sup>48</sup> wherein no exposure concentration *or* duration is considered to be without some level of carcinogenic risk. In the absence of data describing the mode of action (information about how a chemical produces cancer), EPA chooses to be health conservative and uses the same linear low dose extrapolation to estimate cancer risk. In these instances, and especially when the exposure is for much less than a lifetime, this application produces an appreciable amount of health conservatism in risk assessments in which the cancer potency factor derived from a lifetime exposure is used. Thus, and especially for chemicals for which the cancer mode of action is not known, this information gap introduces profound uncertainty in estimating risks from less-than-lifetime exposures.

---

<sup>47</sup> <https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-3>

<sup>48</sup> Explained in Sections 8.4.1 and 8.9.  $c$  is concentration,  $t$  (time) is duration.

## 8.12. Cancer Risk Potency Factors Cannot Quantify Risk

EPA develops cancer slope factors and states that their potency factors cannot be used to quantify risk. Further, ATSDR uses EPA's cancer potency factors and states that their use does not indicate true risk.

The PHA recognized this principle stating,

““Because of the uncertainties and conservative assumptions inherent in deriving the cancer slope factors, this is only an estimate of risk; the true risk is unknown, and might be as low as zero (ATSDR 2005).” (ATSDR, 2017a).

What cancer potency values can be used for is to demonstrate that an exposure might results in a risk of cancer that is so low as to be in the “acceptable” range of risks.

### 8.12.1. ATSDR's Cancer Risk Evaluation Guideline (CREG) Values Cannot Quantify Risk

The Cancer Risk Evaluation Guideline (CREG) values are comparison values for life-long exposures that are derived from EPA cancer slope factors. CREG values identify a concentration in air or water at a theoretical cancer risk level of one in one million from a lifetime exposure. ATSDR's oral CREG values apply to lifetime exposure via soil and water ingestion. As described in the ATSDR Public Health Assessment Guidance Manual (ATSDR, 2005), CREG values are developed for drinking water to identify of a concentration at the tap representing a 1 in one million ( $10^{-6}$ ) risk, based on EPA's oral cancer slope factor, when consumed by a 70 kg human drinking 2 liters of such water per day for a 78-year lifetime<sup>49</sup>. This level of risk is one hundred-fold lower than the maximum level of risk deemed acceptable ( $10^{-4}$ , or one in ten thousand). The PHA inappropriately compares air and water contaminant concentrations from short duration exposures to CREG values. These comparisons in the PHA do not acknowledge that when such comparisons are made that ATSDR has indicated that the true risk might be as low as zero.

EPA develops a conceptually similar value, called the Drinking Water Unit Risk value. This value is presented as the risk per microgram per liter of drinking water, calculated based on EPA oral cancer potency factor and assumptions about drinking water ingestion and body weight. Because both CREG values and Drinking Water Unit Risk values are based on EPA cancer slope factors, EPA and ATSDR have each stated that that the true risk “may be as low as zero.” Thus, CREG values and drinking water unit risk values have no prognostic value in developing quantitatively reliable estimates of risk.

Similarly, MCLs are not based on cancer risk quantitation. Thus, exceedances of MCL values also cannot be used to support contention of an increased cancer risk. For a complete discussion of MCL values, refer to Section 11.

---

<sup>49</sup> [https://www.atsdr.cdc.gov/pha-guidance/conducting\\_scientific\\_evaluations/screening\\_analysis/screening\\_levels\\_used\\_by\\_ATSDR.html](https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/screening_analysis/screening_levels_used_by_ATSDR.html)

## 9. HAZARD QUOTIENT AND HAZARD INDEX VALUES

Hazard Quotients (HQ) are used in non-cancer screening-level risk assessment and express the ratio of an exposure to an acceptable level of exposure, such as an MRL or an EPA Reference dose. An HQ value is developed for a single chemical by dividing the exposure by a measure of an acceptable level, where an acceptable level is typically an oral reference dose, and inhalation reference concentration or a MRL value.

$$\text{HQ} = \text{E} / \text{AL}$$

HQ is a unitless ratio value because both exposure and acceptable level values are in units of dose. The Exposure is measured, estimated, or assumed for a particular site, and the Acceptable Level values used in the PHA are EPA Reference values or ATSDR MRL values (even though it is established that these values cannot be used to indicate risk if their values are exceeded). When Exposure goes up, the HQ goes up; when the Acceptable Level value goes down, the HQ goes up. Thus, in screening-level assessments including the PHA where exposure is biased toward an increased value and acceptable level values are biased toward a lower value, the resulting HQ values contains compounded bias, resulting in higher (not lower) HQ and HI values.

$$\text{HI} = \Sigma \text{HQ}$$

The Hazard Index is the sum of HQ values for individual chemicals in a mixture. In a screening analysis like the PHA, if HQ or HI values exceed a value of 1, this means that the site, exposure or chemical should be evaluated further as part of the decision-making process. HQ or HI values > 1 do not indicate increased risk. These values are not further evaluated in the PHA.

A HI value is developed for exposures to several chemicals. HI values can be computed for specific organs or tissues by summing the HQ values for each chemical that affects that organ or tissue.

Combining the HQ values to develop an HI value represents addition, where the responses from single chemical add to one another. Under this approach, the assumption is that the chemicals act on the organ or tissue through the same mode of action, which has a substantial impact on confidence. EPA (2023) wrote, “[c]onfidence in assessments that rely on dose-additive methods is strengthened if some degree of similarity in toxicokinetic and/or toxicodynamic action is demonstrated among the chemicals in the mixture being evaluated.” Whether chemicals do act through the same mode of action is often unknown, but HQ values are still combined for the health protective purpose of risk assessment. In this case, the summing of HQ values to develop an HI value in the absence of mode of action knowledge represents a conservative assumption which is acknowledged by EPA (2000d). This means that if they don’t act through the same mode of action, then the summed response may be less than what is predicted by adding their responses together. Summing HQ values to develop an HI value in the

absence of knowledge of the mode of action is not contradicted, but should be acknowledged as being health-protective.

This is the approach applied in the PHA to evaluate the risks for non-cancer effects.

HQ and HI values are useful in risk assessment, but they must be further interpreted and not taken to represent risk. HQ and HI values are comparisons of exposure, not risk. The numerical value of an HQ value represents a ratio of exposures; it is not an indication of risk for reasons including the lack of dose response information contained in the value.

In a screening analysis like the PHA, if HQ or HI values exceed a value of 1, this means that the site, exposure of chemical should be evaluated further as part of the decision-making process. HQ or HI values greater than 1 do not indicate risk. When HQ or HI values exceed 1, the ATSDR's Public Health Evaluation Guidance Manual (ATSDR, 2005) instructs the conduct of an "in-depth toxicological evaluation" (described in Section 9.2). Briefly, this guidance indicates an evaluation of the underlying toxicity data supporting the risk value to which the exposure is compared. However, the PHA failed to acknowledge a need to more carefully evaluate toxicity data, writing, "HI values greater than 1 do not mean that health effects will occur, only the need to evaluate exposure levels further to determine the potential for the combined effect of the chemicals that could be affecting the organ system in the body and by the same mechanism of action." (ATSDR, 2017a). The PHA failed to acknowledge the value of a further evaluation of the toxicological issues associated with the developed HQ or HI value.

In the screening approach, often the reasonable maximal (ultra conservative) exposure is used as the "E" and the RfD value is used as the "AL" in the HQ equation. Here, if the screening level evaluation indicates that risk is unlikely (that the magnitude of the HQ value does not indicate an increased level of concern), the assessment can proceed through the remainder of risk characterization and into risk management. However, if a screening level analysis failed to demonstrate that the concern for risk is acceptable, the assumptions, extrapolations, and uncertainties involved will be examined and their impact on the screening level value should be / will be examined. It may be that the consideration of these factors, issues and parameter values will result in a modification of the initial conclusions based on the screening level assessment. Those modifications may result in a revised conclusion that risk is unlikely or may confirm/support the conclusion that the assessment's initial (screening level) conclusion that risk cannot be ruled out. In either case, the "characterized" risk evaluation will be forwarded to risk managers for implementation. EPA (2000c) writes, "[t]he length of a risk characterization for a screening assessment, for example, will not likely be very long due to little data or scientific knowledge."

### 9.1. Hazard Quotient and Hazard Index Values Address Only Exposure.

HQ and HI values address only exposure, not risk, because of the lack of dose response data. These values place a site-specific, and often highly unlikely exposure in the context of an exposure correlating to a health-protective reference value which is set above levels that may be adverse. HQ and HI values are developed to prioritize chemicals and sites for further evaluation. They do not represent risk and should not be interpreted to do so.

EPA (1986a) writes,

“If the exposure level (E) exceeds this threshold (i.e., if E/RfD exceeds unity), there may be concern for potential non-cancer effects. As a rule, the greater the value of E/RfD above unity, the greater the level of concern. Be sure, however, not to interpret ratios of E/RfD as statistical probabilities.”

If the HQ value is greater than 1, the factors influencing the value of the HQ need to be examined.<sup>50</sup> Because dose response is the central tenet of toxicology, and because risk values are based on toxicological data, it is critical to understand the toxicological dose response of the effect serving as the basis for the risk value. EPA confirms that the derived HQ and HI values do not represent dose response evaluations, and clarifies that they cannot be construed to represent a risk.

Similarly, ATSDR’s Public Health Assessment Guidance Manual (ATSDR, 2005) agrees that the HI and HQ do not represent risk. The Guidance Manual characterizes the health guidelines (the acceptable level values) used in the screening analysis as “extrapolated doses” further adjusted to ensure that they are “amply protective.” When the exposure exceeds such guideline values, ATSDR advises an analysis of the actual data (e.g., from journal articles) that serve as the basis for the health guideline, and to compare the conditions of exposure in the underlying toxicity studies to the conditions of site-specific human exposure to determine “whether differences between study data and the exposure scenario being evaluated make health effects more or less likely.”

## 9.2. How Should HQ Values Be Interpreted?

EPA (1986b) has described the hazard index, stating: “[t]he hazard index provides a rough measure of likely toxicity and requires **cautious interpretation**.

The hazard index is only a numerical indication of the nearness to acceptable limits of exposure or the degree to which acceptable exposure levels are exceeded. As this index approaches unity,

concern for the potential hazard of the mixture increases. If the index exceeds unity, the concern is the same as if an individual chemical exposure exceeded its acceptable level by the same proportion. The hazard index does not define dose-response relationships, and its numerical value should not be construed to be a direct estimate of risk.” (emphasis added).

EPA advocates that when an HQ value exceeds 1, the assumptions, uncertainties, and extrapolation steps involved should be evaluated and “a hazard index or quotient of ~1.0 indicates that it is unlikely for even sensitive populations to experience adverse health effects.”<sup>51</sup>

ATSDR writes, “Once you have your HQ, compare it to 1. HQs less than 1 indicate that a non-cancer hazard should not be an issue. When an HQ is greater than 1, retain those contaminants and conduct an

Since every assessment carries uncertainties, a simplified numerical presentation of risk is always incomplete and often misleading (EPA, 1995).

---

<sup>50</sup> An examination like this would include issues like the assumptions, extrapolations, and uncertainties relating to both the estimated exposure and the risk value to which the exposure is compared.

<sup>51</sup> Quoted text from EPA (1989)”

in-depth toxicological analysis. In other words, an HQ above 1 means that there is an exceedance of the non-cancer health guideline.”<sup>52</sup> Public Health Assessment Guidance Manual (ATSDR, 2005) recommends<sup>53</sup> a deeper dive including an “in-depth toxicological effects analysis” if an HQ value exceeds 1. Some components of that evaluation include:

- Identify and review relevant data from studies used to develop health guidelines (e.g., ATSDR Tox Profiles [MRL Worksheet], EPA IRIS);
- Review original journal articles that serve as the basis for health guideline development;
- “If you feel it’s needed, you might review the basis (applicability and strength) of the study data used to generate the health guidelines. This review provides perspective on how strongly the supporting toxicologic data suggest that harmful exposures might occur under your site-specific exposure conditions.”;
- Compare the site-specific doses and concentrations to observed study effect levels, computing a Margin of Exposure;
- Consider the study applicability to site-specific exposures (e.g., duration, exposure route, chemical form);
- Examine uncertainty.

One way to further interpret the results of an HQ or HI value is to use the Target Organ Toxicity Dose (TTD) method to develop HI values for multiple chemicals acting on specific organs or tissues. An additional evaluation should consider whether the chemicals grouped together by target organ act in the same way, on the same biological components and processes within that target organ.

**Further context can be given to HQ and HI values by evaluating the extent that the effect increases when the dose increases.** EPA’s Risk Assessment Guidance for Superfund (EPA, 1989) frames this issue:

“If the exposure level (E) exceeds this threshold (i.e., if E/RfD exceeds unity), there may be concern for potential non-cancer effects. As a rule, the greater the value of E/RfD above unity, the greater the level of concern. Be sure, however, not to interpret ratios of E/RfD as

statistical probabilities; a ratio of 0.001 does not mean that there is a one in one thousand chance of the effect occurring. Further, it is important to emphasize that the level of concern does not increase linearly as the RfD is approached or exceeded because RfDs do not have equal accuracy or precision and are not based on the same severity of toxic effects. Thus, the slopes of the dose-

For two or more chemicals that affect the same organ, tissue or system, but impact different functions in that organ, tissue or system, combining HQ values from these chemicals within the same organ, tissue or system represents an uncertainty and a conservative choice in TTD-based evaluations.

---

<sup>52</sup> [https://www.atsdr.cdc.gov/pha-guidance/conducting\\_scientific\\_evaluations/epcs\\_and\\_exposure\\_calculations/hazardquotients\\_cancerrisk.html#:~:text=Once%20you%20have%20your%20HQ,the%20non%2Dcancer%20health%20guideline.](https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/epcs_and_exposure_calculations/hazardquotients_cancerrisk.html#:~:text=Once%20you%20have%20your%20HQ,the%20non%2Dcancer%20health%20guideline.)

<sup>53</sup> ATSDR’s Public Health Assessment Guidance Manual advises a similar approach to the evaluation of cancer effects. (ATSDR, 2005).

response curve in excess of the RfD can range widely depending on the substance.” (emphasis in original).

Just because two or more chemicals act on the same organ or system, combining their HQ values to determine an HI value may not be justified. EPA (2000c) instructs the value of knowing a bit more about what effect a chemical brings about and its mode of action, considered as “toxicologic similarity”:

“The Hazard Index method is specifically recommended only for groups of toxicologically similar chemicals that all have dose-response data. In practice, because of the common lack of information on mode of action and pharmacokinetics, the requirement of toxicologic similarity is usually relaxed to that of similarity of target organs (U.S. EPA, 1989).”

### 9.3. Chronic Reference Values Over-Estimate the Potential for Health Effects Resulting from Less-Than-Lifetime Exposures

ATSDR’s PHA (ATSDR, 2017a) reported that 85% of the Marines-in-training had a Camp Lejeune residence time of less than three years, with a median of 18 months for Navy and Marine personnel (ATSDR, 2017b). However, ATSDR’s PHA used a three-year exposure duration in risk calculations, which results in an over-estimation of exposure and resulting risk for 85% of the relevant population. Further details of the duration analysis are not presented in the PHA.

Chronic reference values pertain to lifetime or other long-term exposures and, thus, are overly protective if used to evaluate the potential for adverse health effects resulting from substantially less-than-lifetime exposures. For such situations at Superfund sites, EPA’s Provisional Peer Reviewed Toxicity Values program calculates subchronic duration toxicity values specifically for subchronic exposure durations, using the method outlined above for chronic RfDs.<sup>54</sup> However, the PHA relied on EPA’s Chronic duration reference values (see ATSDR, 2017a, Tables 5a and 5b) to develop HQ and HI values. In EPA’s Risk Assessment Guidance for Superfund (EPA, 1989), EPA acknowledged the value of subchronic reference values in evaluating risks at Superfund sites (which would include Camp Lejeune) for which the exposure is less-than-lifetime:

“On the other hand, for evaluating potential noncarcinogenic effects of less-than lifetime exposures, do not compare chronic RfDs to short-term exposure estimates, and do not convert short-term exposures to equivalent lifetime values to compare with the chronic RfDs. Instead, use subchronic or shorter-term toxicity values to evaluate short-term exposures. **Check that the estimated exposure duration is sufficiently similar to the duration of the exposure in the study used to identify the toxicity value to be protective of human health (particularly for subchronic and shorter-term effects).** A toxicologist should review the comparisons. In the absence of short-term toxicity values, the chronic RfD may be used as an initial screening value; i.e., if the ratio of the short-term exposure value to the chronic RfD is less than one, concern for potential adverse health effects is low. If this ratio exceeds unity, however, more appropriate short-term

---

<sup>54</sup> <https://www.epa.gov/pprtv/basic-information-about-provisional-peer-reviewed-toxicity-values-pprtvs#basicinfo> and EPA (1989 - Risk Assessment Guidance for Superfund, Part B).

toxicity values are needed to confirm the existence of a significant health threat.” (emphasis added).

Failing to reconcile or even acknowledge this duration-based discrepancy when developing HQ or HI values for a less-than-lifetime exposure represents a health conservative approach and serious oversight.

Further details on the interpretation of HQ and HI values are provided in Section 10.7.

## 10. THE RESULTS OF A RISK ASSESSMENT MUST BE PRESENTED AND INTERPRETED IN THE CONTEXT OF THE PURPOSE FOR WHICH THE ASSESSMENT WAS CONDUCTED.

Several important concepts should be placed front and center when interpreting the results of a risk assessment activity, including ATSDR's PHA (ATSDR, 2017a).

### 10.1. Risk Assessments are Decision-Making Tools, Not Point Estimates

By 1989, the U.S. government recognized the complexities of characterizing and communicating risk information, specifically in using point estimates of risk. The Executive Office of the President (USCEQ, 1989) wrote, "point estimates of risk, including expected values, can be misleading since they hide the existence of uncertainty and variability." Similarly, EPA (1989) wrote, "[t]he [Reference dose] is generally considered to have uncertainty spanning an order of magnitude<sup>55</sup> or more, and therefore the [reference dose] should not be viewed as a strict scientific demarcation between what level is toxic and nontoxic."

Risk assessments are decision-making tools, not precise analyses of actual or measurable risk, so their focus should remain on how best to inform the ultimate goal—risk reduction—rather than on generating complex distributions of possible risk estimates.

- CRARM, 1997

Moreover, EPA (2000c) clarified that risk characterizations are not only about science but also about the policy decisions that are included in the risk assessment. Similarly, the NRC (1994) has recognized the importance of risk assessments in context:

"Numerical estimates should never be separated from the descriptive information that is integral to the risk assessment. For decisionmakers, a complete characterization (key descriptive elements along with numerical estimates) should be retained in all discussions and papers relating to an assessment used in decision-making. Differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk management decisions in cases with ostensibly identical quantitative risks; i.e., the "number" alone does not determine the decisions."

Therefore, making a decision about the acceptability of risk from exposures at Camp Lejeune cannot be made on the basis of numerical values for Hazard Indices, upper bound estimates of cancer risk, or by

---

<sup>55</sup> An order of magnitude is 10-fold. The square root of 10 is 3.16, dividing the order of magnitude equally around the RfD, this would represent a range from (RfD / 3.16) to (RfD X 3.16). Inasmuch as the acknowledged range of uncertainty around the RfD is three-fold, indicating that exposures as much as three-fold above the RfD fall within the accepted range of uncertainty. This is especially important when RfD (or RfC) values are used as the "acceptable limit" value in computing HQ and HI values.

comparison of exposures to MCL values. Values like those presented in the screening analysis represented by the PHA must be accompanied by a discussion of issues like the uncertainties, assumptions, and extrapolations embedded in the assessment. The numerical values presented in the PHA are not point estimates for risk.

## 10.2. Screening Approaches are Worst-Case Scenarios

Screening level assessments like the PHA are conducted as the first step in a continuum of approaches to better understand the implications of exposures. Screening assessments typically include worst-case assumptions, including the reliance on conservative, upper-bound estimates of parameter values. They include conservative, health-protective risk values as if they were gold standards, assuming that risk may be anticipated at exposures even trivially increased over risk values.

Moreover, risk assessments include many parameters included in exposure scenarios (e.g., rate of drinking water ingestion, time spent in a given location, Reference Dose value, cancer slope factor). The estimation of values for many of these parameters is a mathematical exercise, and are combined to reach the risk assessment conclusions.

Where the worst-case value for each of the parameters is used – and the worst-case scenario is unlikely – the likelihood of the outcome becomes highly unlikely. Some of these parameter values are discussed in turn below.

In a probabilistic risk estimation, each time we use a 95% confidence bound value instead of the most likely value for a parameter, we increase the estimated risk by ten-fold.

## 10.3. EPA Reference Values Cannot Be Used to Quantify Risk

Risk values cannot quantify risk. EPA's non-cancer Oral Reference Dose and Inhalation Reference Concentration values and ATSDR's non-cancer MRL values cannot be used to quantify risk. Their definitions clarify that they identify exposures which are **not** expected to be accompanied by risk. When exposures are at or below these risk values, risk is not expected.

EPA defines the reference dose and reference concentration values as those likely to be without increased risk when encountered for a lifetime.<sup>56</sup> There is no method that uses reference values to quantify risk; reference values address exposures unlikely to include risk. EPA recognizes that these values embody a margin of safety, and cautions that these values are not “bright lines” demarking exposures anticipated to be without risk:

---

<sup>56</sup> Integrated Risk Information System (IRIS) Glossary, at: [https://sor.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary](https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary)

- “The current approach for deriving RfDs does not provide the risk manager with insight concerning the potential hazard posed by a chemical when exposures exceed the RfD.” (Swartout<sup>57</sup> et al., 1998).
- “The NOAEL [threshold] procedure for calculating the RfD does not include the estimate of error or variability in the RfD; thus it is unclear how to express the potential consequences of excess exposure.” (Teuschler<sup>58</sup> et al., 1999).
- “Current RfD-based risk characterizations do not provide information on the fraction of the population adversely affected by a given dose or any other direct measure of risk.” (NRC, 2009a; EPA, 2000c).
- “Reference values are not predictive values; they provide no information about risks at higher exposure levels.” (EPA, 2022a).
- Specifically, EPA<sup>59</sup> wrote: “In general IRIS values [reference doses, reference concentrations, inhalation unit risk values, oral slope values] cannot be validly used to accurately predict the incidence of human disease or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental doses. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposure to a chemical influence the occurrence and extent of human disease.”

#### 10.4. ATSDR’s MRL Values Cannot Be Used to Quantify Risk

ATSDR recognized that “[MRL values] are set **below** levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance-induced effects” (emphasis added).<sup>60</sup> ATSDR emphasized these concepts in a website providing additional information on MRLs,<sup>61</sup> writing:

“These substance-specific estimates [MRL values], which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.”

---

<sup>57</sup> Mr. Swartout was employed in EPA’s Office of Research and Development, Cincinnati, OH.

<sup>58</sup> Ms. Teuschler was employed in EPA’s Office of Research and Development, Cincinnati, OH.

<sup>59</sup> <https://assessments.epa.gov/documents/&deid%3D2776>

<sup>60</sup> Minimal Risk Levels (MRLs) – For Professionals, at: [https://www.atsdr.cdc.gov/minimal-risk-levels/php/about/index.html#:~:text=Exposure%20durations,Chronic%20\(365%20days%20and%20longer\)](https://www.atsdr.cdc.gov/minimal-risk-levels/php/about/index.html#:~:text=Exposure%20durations,Chronic%20(365%20days%20and%20longer))

<sup>61</sup> Minimal Risk Levels (MRLs) – For Professionals, at: <https://www.atsdr.cdc.gov/mrls/index.html>

“MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects.”

Health guidelines (used to evaluate non-cancer health effects) (see descriptions in this table)<sup>62</sup> and cancer risk values (used to estimate cancer risks) (see descriptions in this table) are derived from data in the epidemiologic and toxicologic literature with appropriate uncertainty or safety factors applied to ensure they are set at levels below those that could result in harmful health effects. The values do not represent thresholds of toxicity.<sup>63</sup>

The PHA explains “[a]n MRL should not be used as a predictor of adverse health effects.” (ATSDR, 2017a).

ATSDR also clarified, “[e]xposure to a chemical above the MRL values does not mean a person will have health problems.”<sup>64</sup> Exposure above the MRL equates to a HQ above 1. When HQ or HI values exceed a value of 1, ATSDR (2005) recommends an in-depth toxicological evaluation. The evaluation should include “[c]ompar[ing] the site-specific doses and concentrations to observed study effect levels, computing a Margin of Exposure.” However, such a comparison is absent from PHA, making it difficult to interpret the implication of HI values. The PHA (ATSDR, 2017a, p. 79), itself, acknowledged this limitation of the MRL values, noting, “[a]n MRL should not be used as a predictor of adverse health effects.” It is clear that a comparison of an exposure to an MRL value is not a valid basis for a conclusion of increased risk in the case of an exceedance exposure.<sup>65</sup>

## 10.5. ATSDR’s EMEG and RMEG Values Cannot be Used to Quantify Risk

The PHA, similar to other risk assessments, incorporates Environmental Media Evaluation Guides (EMEGs) and Reference Dose Media Evaluation Guides (RMEGs). RMEG and EMEG values are only screening tools – their application tells us where we need to look more closely. This is in part because EMEGs are derived from ATSDR chronic MRL values and RMEGs are derived from EPA chronic reference values. Issues with both parameters are discussed in Section 10.6.

---

<sup>62</sup> The referenced table describes MRL values: “[MRL values] are set below levels that might cause adverse health effects in most people, including sensitive populations.” Health Guideline values are based on MRL values, Reference values and cancer potency factors; these are identified on page 78 of the PHA (ATSDR, 2017a). The PHA indicates that these values are “comparison Values, “used to determine which chemicals to examine more closely”, not against which to infer risk.

<sup>63</sup> [https://www.atsdr.cdc.gov/pha-guidance/conducting\\_scientific\\_evaluations/epcs\\_and\\_exposure\\_calculations/hazardquotients\\_cancerrisk.html#:~:text=Health%20guidelines%20\(used%20to%20evaluate,for%20oral%20and%20inhalation%20exposures.](https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/epcs_and_exposure_calculations/hazardquotients_cancerrisk.html#:~:text=Health%20guidelines%20(used%20to%20evaluate,for%20oral%20and%20inhalation%20exposures.)

<sup>64</sup> [https://www.atsdr.cdc.gov/minimal-risk-levels/about/index.html#:~:text=Minimal%20Risk%20Levels%20\(MRLs\)%20are%20a%20prediction,data%20on%20human%20health%20effects%20is%20incomplete.](https://www.atsdr.cdc.gov/minimal-risk-levels/about/index.html#:~:text=Minimal%20Risk%20Levels%20(MRLs)%20are%20a%20prediction,data%20on%20human%20health%20effects%20is%20incomplete.)

<sup>65</sup> The ratio of an exposure to an MRL value is an example of a HQ value.

ATSDR (2005) explains the purpose and applicability of EMRG and RMEG values as screening tools, writing:

“When no EMEGs are available, RMEGs serve as a screening tool to be used when conducting an environmental guideline comparison. Like EMEGs, substances found at concentrations below RMEGs are not expected to pose public health hazards and substances found at concentrations above RMEGs require further evaluation before drawing a public health conclusion. RMEGs also serve only as screening values and not indicators of public health hazards.”

In other words, because RMEG and EMEG values are based on EPA reference values and ATSDR MRL values, exceedance of an RMEG or EMEG value does not indicate an increased risk.

## 10.6. Several Issues Common to Many Non-cancer Risk Values

Because EPA Reference Values, ATSDR MRL values, and ATSDR comparison values like EMEG and RMEG values have several characteristics in common, there are caveats that apply to all of these values. Many technical aspects (e.g., whether the critical effect is adverse or not, how the POD is selected) are discussed throughout this report. But there are two characteristics that are especially noteworthy when evaluating their application in the estimation of risk from non-hypothetical exposures: (1) duration; and (2) uncertainties.

### 10.6.1. Chronic Reference Values Over-Estimate Short-Duration Risk

As discussed in Section 9.3, the PHA assumed a health-conservative exposure duration of three years. In reality, the PHA (ATSDR, 2017a) reported that 85% of the Marines in training had a Camp Lejeune residence time less than three years, with a median of 18 months for Navy and Marine personnel (ATSDR, 2017b). Therefore, this results in an over-estimation of exposure and resulting risk for 85% of the relevant population.

In risk assessments, including the PHA, chronic reference values pertaining to lifetime or other long-term exposures are used. Thus, they are overly protective if used to evaluate the potential for adverse health effects resulting from substantially less-than-lifetime exposures. Where less-than-lifetime exposures occur, EPA's Provisional Peer Reviewed Toxicity Values program calculates subchronic duration toxicity values specifically for subchronic exposure durations, using the method outlined above for chronic RfDs.<sup>66</sup> However, the PHA relied on EPA's Chronic duration reference values (see ATSDR, 2017a, Tables 5a and 5b) to perform its assessment. Failing to reconcile or even acknowledge this duration-based discrepancy when developing HQ or HI values for a less-than-lifetime exposure represents a very health conservative approach and it was a serious oversight for the PHA to fail to acknowledge this.

---

<sup>66</sup> <https://www.epa.gov/pprtv/basic-information-about-provisional-peer-reviewed-toxicity-values-pprtvs#basicinfo> and EPA (1989 - Risk Assessment Guidance for Superfund, Part B).

## 10.6.2. Uncertainty Factors Substantially Reduce Risk Values

Uncertainty factors<sup>67</sup> are obviously an issue to be addressed when unpacking point estimates of risk. They are used to bridge gaps in the available data. The use of conservative, health protective values for uncertainty factors contributes to the level of health protection by adding to the margin of safety in risk values. This is done by assigning values for uncertainty factors that are higher than evidence suggests that they should be. Because uncertainty factor values are multiplied together to develop the combined uncertainty factor that is used to extrapolate the point of departure, the level of health protection is likewise over-inflated as uncertainty factors pile on.

Inasmuch as EPA has a mandate and a mission to protect human health, the risk values EPA develops are biased toward including a level of health protection for an adequate margin of safety. For example, EPA<sup>68</sup> wrote:

“To determine the RfD, the concentration for the non-carcinogenic effects from an epidemiology or toxicology study is divided by uncertainty factors (for example, for sensitive subpopulations). This provides a margin of safety for consumers of drinking water.”

## 10.7. Hazard Quotients and Hazard Index Values Cannot be Used to Quantify Risk

As discussed in Section 9, risk assessments employ HQ and HI values as part of the screening exercise. HQ values are screening values developed for single chemicals that evaluate exposure, not risk. In risk assessments, the HQ values for each of the chemicals of interest are summed to determine the HI for exposure. If HQ or HI values exceed a value of 1, this means that the site, exposure or chemical should be evaluated further as part of the decision-making process. However, HQ or HI values greater than 1 do not indicate increased risk and should not be interpreted as such in risk assessments, including the PHA.

The Hazard Index does not define dose-response relationships, and its numerical value should not be construed to be a direct estimate of risk.

(EPA, 1989)

---

<sup>67</sup> Of the four uncertainty factors applied to study-specific data (UFA, UFH, UFS, UFL) only UFA and UFH represent variability and can be quantified on the basis of data, under EPA Risk Assessment methods. UFA and UFH have been divided into toxicokinetic and toxicodynamic components, and reliable data pertinent to these domains can be considered as the basis for quantitative, non-default uncertainty factor values (e.g., EPA’s Data-Derived Extrapolation Factors; EPA, 2014b). When these factors have been quantified, some uncertainty may remain, but EPA advises the use of quantitative values for these factors over continued reliance on default values for the uncertainty factors.

<sup>68</sup> <https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#develop>

### 10.7.1. Hazard Quotient and Hazard Index Values Address Exposure

HQ and HI values address exposure only (see Section 9.1). These values place a site-specific, often highly unlikely exposure in the context of an exposure correlating to a health-protective reference value which is set above levels that may be adverse. These values are developed to prioritize chemicals and sites for further evaluation. They do not represent risk.

- “The hazard index is only a numerical indication of the nearness to acceptable limits of exposure or the degree to which acceptable exposure levels are exceeded.” (EPA, 1986a).
- “The HI cannot be translated into a probability that adverse effects will occur, and it is not likely to be proportional to risk.” (NRC, 2009a).
- “Once you have your HQ, compare it to 1. HQs less than 1 indicate a non-cancer hazard should not be an issue. When an HQ is greater than 1, retain those contaminants and conduct an in-depth toxicological effects analysis. In other words, an HQ above 1 means there is an exceedance of the non-cancer health guideline.”<sup>69</sup>

Instead, HQ and the HI quantify only the relationship between the estimated human exposure and the acceptable exposure value. If the HQ value is greater than 1, the factors influencing the value of the HQ need to be examined.<sup>70</sup> They do not contain dose response information or dose response implications. Because dose response is the central tenet of toxicology, and because risk values are based on toxicological data, it is critical to understand the toxicological dose response of the effect serving as the basis for the risk value.

### 10.7.2. Acceptable Level Values are Biased to Develop Higher Hazard Quotient Values

Additionally, HQ and HI values are a measure of how far the estimated exposure is from an Acceptable Level. Many values adopted as Acceptable Level values are derived from regulatory agencies and encompass a level of health conservatism. The Acceptable Level value may be (1) developed for an effect that is not adverse; (2) on the basis of a response level that is not biologically meaningful; (3) experienced in a small but statistically significant segment of the population; (4) based on a dose representing the lowest 5% of that likely to be associated with the effect; (5) developed for a chronic,

---

<sup>69</sup> [https://www.atsdr.cdc.gov/pha-guidance/conducting\\_scientific\\_evaluations/epcs\\_and\\_exposure\\_calculations/hazardquotients\\_cancerrisk.html#:~:text=Once%20you%20have%20your%20HQ,the%20non%2Dcancer%20health%20guideline.](https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/epcs_and_exposure_calculations/hazardquotients_cancerrisk.html#:~:text=Once%20you%20have%20your%20HQ,the%20non%2Dcancer%20health%20guideline.)

<sup>70</sup> An examination like this would include issues like the assumptions, extrapolations and uncertainties relating to both the estimated exposure and the risk value to which exposure is compared.

lifetime exposure;<sup>71</sup> (6) additionally reduced if there are uncertainties in other areas of the toxicity database; and (7) further reduced if it was based on the results of less-than-lifetime study. For the PHA, ATSDR used EPA chronic Reference values or ATSDR chronic MRL values as the acceptable values. Because the equation is a ratio, when the Acceptable Level value goes down, the HQ goes up. Thus, in HQ-based risk assessments where acceptable level values include a margin of safety, the bias is toward developing higher HQ values in which the level of conservatism is compounded by inclusion of exposure estimates biased toward higher levels.

### 10.7.3. Dose Response Information is Key to Interpreting Hazard Quotient Values

The full dose response relationship is key to the interpretation of the HQ. Different effects may have dose-response relationships with different slopes (see Figure 8). In contrast, in risk assessment, the slope of the HQ is fixed at a slope of one for every effect,<sup>72</sup> for every chemical. Therefore, for every doubling of the exposure, the HQ value doubles. But, this should not be assumed to be true for the dose response of the actual effect.

Evaluating the true slope of the dose response relationship for the effect that serves as the basis for the acceptable level is informative. For example, the dose response data for thymus weight (Keil et al., 2009) that serves as a basis for EPA reference dose for TCE provide an instructive example. Those data indicate that (as expected) thymus weight decreases with increasing dose; and that the dose ten-fold higher than the point of departure dose decreased thymus weight by an additional 30%. For this example, an HQ value of 10<sup>73</sup> is accompanied by a 30% (0.3-fold) increase in the effect. So, the slope of the HQ is 1 while the slope of the measured effect is 0.03. This information adds quantitative perspective to the interpretation of HQ and HI values developed in the PHA. This comparison was not performed in the PHA.

### 10.7.4. All Hazard Quotient Values Are Not Equal

A further concern that should be evaluated in risk assessment is a uniform use of HQ values to develop the HI. To determine the HI value, the HQ values are summed. This is true even though HQ values may be based on Acceptable Level values derived from effects of varying biological significance, at different

---

<sup>71</sup> Most acceptable level values used in HQ calculations are for the “chronic” or lifetime duration. EPA’s Risk Assessment Guidance for Superfund Volume A (EPA, 1989) addressed the use of chronic values directly, writing, “[t]he chronic RfDs described above pertain to lifetime or other long-term exposures and may be overly protective if used to evaluate the potential for adverse health effects resulting from substantially less-than-lifetime exposures.” (EPA, 1989 RAGS Part A).

<sup>72</sup> Section 9 describes HQ and HI values. HQ is simply the ratio of the exposure to the Acceptable Level.

<sup>73</sup> The HQ value is 10 because of the 10-fold increase in dose or exposure.

levels of response, and which may include appreciably different uncertainty factors. In other words, the reality of the effect of the chemicals may not be the sum of the chemicals as reflected in the HI value.

ATSDR recommended a more instructive comparison of the exposure to the point of departure for the effect. This avoids complications introduced when different effects have different uncertainty factors. ATSDR wrote, “[i]f the estimated dose [exposure] of the individual chemicals are less than one-tenth of their respective NOAELs, then significant additive or interactive effects are unlikely, and no further evaluation is necessary.” (ASTDR, 2005).<sup>74</sup> If the estimated exposure is within ten-fold of the POD dose, this triggers additional investigation. Using the POD values for Camp Lejeune chemicals of interest taken from respective ATSDR Toxicological Profile documents and worst-case exposure estimates from the PHA, this level is exceeded only by TCE. However, the PHA failed to include the necessary information to support this additional investigation for effects other than the critical effect for the risk value (see ATSDR, 2017a, Tables 5a and 5b).

Another concern emerges when the duration of the toxicity study is not aligned with the duration of the human exposure at the site. As indicated in Tables 5a and 5b of the PHA (ATSDR, 2017a), the PHA used MRL and Reference Values that were developed for application to human exposures of up to a lifetime to estimate risks for durations as short or shorter than 18 months.

To fully understand the import of HQ and HI values, additional pertinent information should be presented. EPA has established risk characterization guidance and ATSDR has established the in-depth toxicological evaluation guidance to help interpret HQ and HI values. Such a presentation and discussion are absent from the PHA, and so, there is no way to determine a level of concern associated with the HQ and HI values presented.

#### 10.7.5. Additional Issues in the PHA’s interpretation of HQ and HI Values

Following risk assessment guidance, the PHA employed the Target Organ Toxicity Dose (TTD) approach to developing HQ and HI values.<sup>75</sup> Under this approach, the Acceptable Level values for multiple organs or tissues are included in addition to the Acceptable Level value for the most sensitive organ or tissue. For mixtures of chemicals, TTD-based HQ values are segregated by organ or tissue, then summed, regardless

---

<sup>74</sup> ATSDR’s suggested in-depth toxicological evaluation recommends that findings from the original study be examined and comparisons made to the point of departure. The PHA’s Tables D-1 and D-2 present “HED [Human Equivalent Dose] NOAEL” and “HEC [Human Equivalent Concentration] NOAEL” values, but these are not point of departure values because they are not the doses in the underlying toxicity study, HEC and HED values are extrapolated from results in the underlying toxicity studies. (ATSDR, 2017a).

<sup>75</sup> The PHA used Target Organ Toxicity Dose values (ATSDR, 2004) to compute HQ and HI values for many effects. These TTD values should be the candidate reference dose values developed for the lesser-sensitive effects, previously described as candidate critical effects. The PHA does not identify the sources of TTD values, or their underlying experimental studies.

of whether the organ or tissue was the most toxicologically sensitive or not (Mumtaz et al., 1997; Lipscomb et al., 2010; ATSDR, 2018).

Despite guidance from EPA and ATSDR itself, the PHA inappropriately drew conclusions about risk from the HQ and HI values. The PHA estimated exposures for two locations at Camp Lejeune and presented their HQ and HI values. The PHA (ATSDR, 2017a, p. 29) concluded: “[t]he HI data indicate higher health risk at Hadnot Point than at Tarawa Terrace across all age groups.” However, the HQ and HI values presented in the PHA should not be relied-upon as indicators of risk. Per ATSDR’s Public Health Assessment Guidance Manual (ATSDR, 2005), they should be further evaluated prior to being used to support conclusions. The PHA’s conclusions of risk from the results of HQ and HI estimations run contrary to the established definitions and purposes for reference values, MRL values, HQ values and HI values.

Importantly, a risk assessment typically considers conservative overestimations of exposure, and conservative, health-protective risk values. The PHA took the same approach. The values used for exposure and acceptable levels in the HQ equation are worst-case estimates and may not reflect the true exposure scenario of the individuals. For example, many values used by ATSDR in estimating exposure for the PHA come from EPA’s Exposure Factors Handbook (EPA, 2011c). ATSDR chose a 95% upper confidence bound on reasonable maximal water ingestion (ATSDR, 2017a, p. 151). This is the amount of water consumed by only 5% of the population rather than a tendency estimate. Regarding Acceptable Level values, a screening analysis will include the chemical’s overall chronic risk value developed as a value applicable for exposures of up to a lifetime. As previously noted, “ATSDR determined that 85% of the active duty Marines and their families lived onbase [sic] for three or fewer years” (ATSDR, 2017a). What this means is that only 15% of the Marines and their families actually lived on base for as long as 3 years, and of that 15%, only 5% consumed as much water as ATSDR estimated in the PHA. This combination of individual worst-case values represents an improbable circumstance that does not apply to the majority of individuals at Camp Lejeune.

To add a layer of conservativeness, for inhalation exposures, the PHA assumed that a person lived in the single residence and never left the residence during the exposure period except for 15 days per year. In reality, most individuals leave their homes at times during the day. The PHA has assumed that the inhalation exposure resulting from showering and bathing is to the maximum concentration predicted by conservative models. Contrary to both data and common sense, the PHA assumed that the concentration did not decline in the residence due to ventilation such as open windows or HVAC systems.

Factors and circumstances like these demonstrate that the exposure values estimated by ATSDR are overestimations of the exposures presumed to have been experienced at Camp Lejeune. This results in the application of lower MRL values than is warranted and concomitantly increase HQ and HI values. Risk assessors are not shackled to use values codified by government agencies; the door is open to use reliable data that are perhaps better aligned with the anticipated duration of exposure to develop valid Acceptable Level values.

## 10.8. Interpreting the Hazard Quotient and Hazard Index Values in the PHA

One must keep in mind that HQ values and the corresponding HI values are not risk estimates. They do not quantify risk, and they do not imply a magnitude of risk. This is because HQ values and HI values do not include information about the magnitude of increase in the response with increasing dose.

EPA (1986b) has described the hazard index, stating:

“The hazard index provides a rough measure of likely toxicity and requires **cautious interpretation**. The hazard index is only a numerical indication of the nearness to acceptable limits of exposure or the degree to which acceptable exposure levels are exceeded. . . . The hazard index does not define dose-response relationships, and its numerical value should not be construed to be a direct estimate of risk.” (emphasis added).<sup>76</sup>

ATSDR (2005) has provided recommendations for interpreting the Hazard Index (see Section 9.2). Many of these recommendations focus on the underlying toxicity study. They include a comparison of the conditions of the human exposure scenario to the dosing scenario in the study, a comparison of the human exposure dose to the study point of departure dose, reviewing the actual dose response for the studied effect, data that inform whether different chemicals act via the same mode of action, etc. However, none of that has been done in the PHA.

### 10.9. Exposure Estimates are Often Worst-Case and Nearly Implausible

A characterization of risk should examine the assumptions, extrapolations, and uncertainties associated with exposure estimates used in the assessment. As with the combined uncertainty factor, the accumulation and integration of conservative assumptions in the overall exposure estimate forces an extraordinary level of conservatism. The use of conservative, unlikely assumptions as multiple steps in developing the exposure assessment leads to an over-inflated exposure estimate that is quite unlikely to represent the true exposure. The PHA's estimates of exposures are no exception. At a minimum, these values should be unpacked and compared to the point of departure values from the experimental studies used to estimate risk values (i.e., to characterize a margin of exposure). Because of lacking data, knowing the actual exposures of individuals at Camp Lejeune to drinking water contaminants is not possible.

### 10.10. Pharmacokinetically-Based Risk Errors for Camp Lejeune Exposures

Plaintiffs' Expert Dr. Gilbert makes the assertion that cancer risk for bladder cancer should be based on an arbitrarily doubled rate of drinking water ingestion “to estimate a more accurate total exposure that takes into account dermal and inhalation exposure from the same water.” This approach to estimating the toxicologically-relevant measure of dose (i.e., the dose at the level of the target tissue) is fundamentally flawed and inexplicable.

---

<sup>76</sup> EPA advocates that when an HQ value exceeds 1, the assumptions, uncertainties and extrapolation steps involved should be evaluated and “a hazard index or quotient of ~1.0 indicates that it is unlikely for even sensitive populations to experience adverse health effects.” (EPA, 1989).

Metabolism is an important aspect of tissue responses. The liver (the site of metabolism) occupies a place in the blood circulation so that the liver “sees” 100% of orally ingested chemicals. However, blood that absorbs inhaled chemicals in the lungs goes to the heart for redistribution, and only 20% of that blood goes to the liver, the rest goes to the tissues before going to the liver.

EPA and ATSDR have applied physiologically based pharmacokinetic models in their assessments for TCE, PCE, and vinyl chloride which provide a reliable basis to estimate tissue-level exposures to parent chemicals or metabolites from oral exposures as well as from inhalation exposures. EPA and ATSDR have used these models and their predictions to establish reference values, MRL values and cancer potency factors.

While accounting for additional exposures (and resulting risk) from sources and routes other than drinking the water that contains these chemicals is most definitely valid, the approach taken in the PHA and by the Plaintiffs’ Experts is not satisfactory. What EPA and ATSDR (outside of the PHA and substantially prior to its development) have done is establish reliable methods to assess oral and inhalation exposures and resulting risk using pharmacokinetic models, not using back-of-the-envelope calculations. Reliance on an arbitrary increase in an oral dose to account for other exposures has no place in a reliable exercise to estimate exposure and risk.

Each of the above concerns, factors, and variabilities must be discussed when unpacking a risk assessment, such as the PHA.

#### 10.11. Properly Bounding Conclusions Reached from Preliminary Analyses is Necessary

The Plaintiffs’ Experts Drs. Hatten, Gilbert, Plunkett, Bird, Mallon and Felsher cite to Rosenfeld et al. (2024), a screening cancer risk assessment for some individuals at Camp Lejeune. There are numerous limitations to Rosenfeld et al. (2024) that must be taken into consideration when interpreting the results of this study. However, the Plaintiffs’ Experts failed to fully take into account these limitations and, thus, misinterpreted the application of Rosenfeld et al. (2024) to the issues addressed in their reports.

Similar to the regulatory risk assessments discussed above, Rosenfeld et al. (2024) incorporated health conservative approaches into the risk assessment. An example of this is the use of an additive approach where the risk of different cancers is added together, as if they act through the same mode of action. This is a conservative assumption and approach for several reasons. First, the chemicals of concern produce different tumors, in different tissues, at different doses, with divergently different biochemical processes and functions. As discussed in Section 9, when the mode of action is unknown, using the additive approach is conservative. Second, the ATSDR’s Interaction Profiles and Toxicological Profiles for the chemicals of concern have addressed the possible chemical interaction types and recognize that the approach is conservative, stating that additivity, or even a less-than additive interaction is justified. The ATSDR does not state in these documents that a synergistic interaction was even possible. Additionally, the PHA concluded that “the additive approach used for Cancer Risk and Hazard Index provides a conservative (health-protective) evaluation of exposure and has been incorporated into this assessment.” (ATSDR, 2017a). This sharply contrasts with Rosenfeld et al.’s statement that “an interaction greater than additive must be considered plausible.”

Additionally, the authors identified limitations in their study and filled the data gaps with worst-case assumptions and maximum numerical values. For example, although the authors acknowledge that the concentrations of contaminants varied, the authors have used the maximum concentrations observed for contaminants at any point during a year. The effect is that the analysis is based on the faulty assumption that the value of contaminants was constant at the maximum measured concentration over the course of the entire year. The authors could have used temporally variable risk factors to take this variation into account, but they chose not to do so. Additionally, the authors base their model on the assumption that all Marines sourced all of their water from the contaminated water treatment systems, when that was not the case. Further, the authors developed conservative estimates of oral, dermal, and inhalation exposures from these concentrations. The authors used theoretical upper bound estimates of cancer potency in a screening approach to estimate cancer risk at Camp Lejeune. The effect of this assumption is that the authors have averaged the estimated upper bound cancer risk from each of three geographically distinct areas to estimate a “basewide” cancer risk. This incorrectly assumes that an individual at Camp Lejeune would have an exposure represented by the ratio of water output from each plant divided by total water output for the base representing (1) the Hadnot Point water treatment plant, (2) the Holcomb Boulevard water treatment plant, and (3) the Tarawa Terrace water treatment plant. Given that this scenario represents a highly unlikely occurrence, it is equally unlikely that the estimate of a “basewide” cancer risk as developed by Rosenfeld et al. (2024) represents anything but speculation.

In addition, the authors have inadvertently led the reader to think that a one in one million risk is the level established for risk acceptability. The authors’ portrayal of a risk above one in one million as representing an unacceptable risk is unsubstantiated and incorrect. In an attempt to provide support, the authors have erroneously cited EPA (2021) as the source for this misstatement. EPA (2021) does not establish or discuss a de minimis risk level. Instead, EPA (2021) reiterates that a risk range of one in one million to one in ten thousand is an acceptable risk range for Superfund sites, which includes Camp Lejeune.

Another limitation preventing a complete interpretation of the study is that Rosenfeld et al. (2024) did not include important details regarding the data employed. This includes, among other things, a definition of the population, and information describing whether the maximum values for all contaminants were reached at the same time. These issues, and the failure to discuss important assumptions about human activity patterns, result in erroneous and misleading statements in the paper. For example, Rosenfeld et al. (2024), states “[f]igure 4 demonstrates that, from 1980 to 1984, 1 month of working on the base could result in a [risk] greater than [the] 1 in a million de minimis risk value.” Rosenfeld’s data<sup>77</sup> failed to provide any basis for this statement. First, a “1 in a million de minimis risk value” is not a risk value recognized by EPA for Superfund sites including Camp Lejeune. EPA’s Superfund program (EPA, 1991b) identifies a risk of one in one million as being within the range of cancer risks acceptable at Superfund sites. Second, Rosenfeld et al.’s own data demonstrated that different water treatment plants on Camp Lejeune have different drinking water concentrations and supply different geographic areas of the base. This results in geographically distinct exposures and, thus, geographically different risks. In fact, the results of Rosenfeld et al. recognize this as areas supplied by the Holcomb

---

<sup>77</sup> CLJA\_RosenfeldSubpoena\_000000001

Boulevard treatment plant and the Tarawa Terrace treatment plant were shown to have a theoretical upper bound cancer risk within the Superfund acceptable range of risks. Third, the authors conjectures that a one-month exposure period may be sufficient to increase cancer risks based on the erroneous assumption that the contaminants (perhaps all the contaminants) attained their maximum concentrations during this hypothetical one-month period. For these and other reasons, the authors' statement regarding a potentially increased cancer risk for working on Camp Lejeune for one month between 1980 and 1984 is a misinterpretation of the risk assessment and is unsubstantiated by the text, supporting data, and references.

Unlike the PHA (ATSDR, 2017a), Rosenfeld et al. (2024) failed to acknowledge that when using theoretical upper bound cancer potency factors (i.e., Inhalation Unit Risk and Oral Cancer Slope Factor values) to estimate the risk of exposures, the true risk may be "as low as zero." EPA (2003) and ATSDR (2005). This, and other issues including those identified herein, strongly weigh against any use of Rosenfeld et al. (2024) to characterize risk for individuals at Camp Lejeune.

Notably, even under the erroneous assumptions and conservative approaches and values used by Rosenfeld et al. (2024), the results demonstrate that exposures to water from the Holcomb Boulevard treatment plant and the Tarawa Terrace treatment plant were not associated with risks that exceeded the Superfund Target cancer-risk range of one in ten thousand. Rosenfeld et al. (2024) found that only for the Hadnot Point water treatment system and only for a narrow time span does the theoretical maximum cancer risk for Marines exceed one in ten thousand (shown graphically as approximately 140 per million, or 1.4 per ten thousand). Given the issues identified above, even this limited determination of risk above EPA risk range is unreliable.

The methods used and results presented by Rosenfeld et al. (2024) must be understood in the context of an understanding of the level of conservatism embodied in the authors' assumptions. Without such information, numerical estimates of cancer risk and statements indicating a minimum duration (e.g., one month, three months) associated with an increased cancer risk are not conveyed in their proper context. These authors do not interpret their findings as indicative of causation, but characterized their risk assessment as a reasonable effort that "offers conservative estimates for evaluating cancer risk." The authors acknowledge the value of their results in identifying health conditions and exposures worthy of added attention. The results are, in fact, screening level risk estimates, and their numerical values invite further consideration of conditions that relate to plaintiff specific exposures and risks. However, risk estimates such as these, in that they are based on conservative risk values, are acknowledged by EPA and ATSDR as being of no prognostic value in informing causation (ATSDR, 1993; EPA, 2003). Rosenfeld et al. (2024) does not acknowledge this at all, allowing the reader to draw an erroneous conclusion to the contrary and leading the Plaintiffs' Experts to use the study inappropriately. Of the Plaintiff Experts citing to Rosenfeld et al. (2024), only Drs. Bird and Felsher acknowledge that the Rosenfeld study even has limitations. Even then, the critique is confusing. Drs. Bird and Felsher mention the limitations of "cancer-slope calculations", but Rosenfeld et al. (2024) does not calculate cancer slope factors, only cancer risk. So, it is fair to say that neither the authors of Rosenfeld et al. (2024) nor the Plaintiffs' Experts acknowledge the full limitations of Rosenfeld et al. (2024).

## 11. MAXIMUM CONTAMINANT LEVEL VALUES CANNOT BE USED TO QUANTIFY RISK

Under the Safe Drinking Water Act (SDWA), Congress has mandated that EPA identify and regulate the concentration of contaminants in public water systems.<sup>78</sup>

EPA (2018) defines MCL-G and MCL values:

- Maximum Contaminant Level Goal (MCLG) - The level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals.
- Maximum Contaminant Level (MCL) - The highest level of a contaminant that is allowed in drinking water. MCLs are set as close to MCLGs as feasible using the best available treatment technology and taking cost into consideration. MCLs are enforceable standards.

MCL values are set forth by EPA to ensure that exposures at or below the designated threshold do not pose a discernible risk. These values are designed with the objective of mitigating potential risk to populations, rather than

The use of values like the Maximum Contaminant Level to estimate the risk of disease is inappropriate.

addressing the likelihood of risk resulting from an excess exposure to any individual. It is important to note that surpassing an MCL does not indicate risk. I am not aware of any guidance that establishes the validity or presents a method to use MCL values in the quantification of risk or causality for individuals).

The MCL values developed by EPA under the under the SDWA have their basis in health risk assessment practices, such as the development of oral reference dose values (for which EPA says that exceedances thereof should not be misconstrued to automatically indicate increased risk). The term “adequate margin of safety” is established in the SDWA (42 U.S.C. § 300g-1 (1996)) to indicate that these values are set at levels lower than those that might cause risk:

§300g–1. National drinking water regulations

(b) Standards

(4) Goals and standards.—

(A) Maximum contaminant level goals.—Each maximum contaminant level goal established under this subsection shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows *an adequate margin of safety* (emphasis added).

---

<sup>78</sup> “Understanding the Safe Drinking Water Act: at: <https://www.epa.gov/sites/default/files/2015-04/documents/epa816f04030.pdf>

MCL values should be set as close to MCL-G values as feasible, and MCL-G values for chemicals that can cause cancer will be set to zero. In establishing these levels, EPA considers the increased sensitivity of specifically identified subgroups including “[t]hose with compromised immune systems and chronic diseases.”<sup>79</sup>

Relative to chemical interactions possible from a multi-chemical exposure via drinking water, EPA (Fed. Reg. 50, 46895 (1989)) wrote, “In addition, the application of the uncertainty factor and 20 percent drinking water contribution helps to take into account possible additive or synergistic effects and the possible high exposure portion of the population.” This thought was carried through to the 1989 notice, where EPA (Fed. Reg. 54, 22069, (1989) again wrote, “The use of uncertainty factors accounts for intra- and interspecies variability, the small number of animals tested compared to the size of the exposed population, sensitive subpopulations and the possibility of synergistic action between chemicals.”

Basing the MCL value on a reference dose value represents one of the health-conservative practices that EPA employs to fulfill its mission of safeguarding the health of the American populace. EPA's drinking water standards hinge upon conservative IRIS risk values, conservative assumptions regarding drinking water consumption, and conservative assumptions regarding additional non-drinking water chemical exposures. Specifically, EPA guides<sup>80</sup> that an MCL value should be set at a concentration representing one-fifth (20%) the concentration that would deliver the reference dose quantity of a chemical via the drinking of finished drinking water (tap water) to a person weighing 70 kilograms and drinking 2 liters of tap water per day for 70 years. The four-fifths reduction (which is called the Relative Source Contribution factor by EPA) is because EPA assumes that 4/5 of the total daily dose would come from sources other than the oral ingestion of drinking water (e.g., drinking or eating other materials containing the chemical or breathing air contaminated with the chemical,<sup>81</sup> which may occur by volatilization from water during drinking, bathing showering, etc.).

The dose (in units of milligrams per kilogram body weight per day) a person gets from drinking water is influenced by three things:

- the concentration of the chemical in the water,
- how much the person weighs, and
- how much water the person drinks in a day.

---

<sup>79</sup> <https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#:~:text=After%20reviewing%20health%20effects%20data,health%20risk%20to%20sensitive%20subpopulations:>

<sup>80</sup> [https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#:~:text=The%20relative%20source%20contribution%20is,example%2C%20food%2C%20inhalation\):](https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#:~:text=The%20relative%20source%20contribution%20is,example%2C%20food%2C%20inhalation):)

<sup>81</sup> [https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#:~:text=The%20relative%20source%20contribution%20is,example%2C%20food%2C%20inhalation\):](https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants#:~:text=The%20relative%20source%20contribution%20is,example%2C%20food%2C%20inhalation):)

While we can compare an exposure to a dose associated with the MCL, inferences of risk when the MCL is exceeded are highly uncertain. Statements like “The concentration was six times higher than the MCL” carry no weight when estimating risk. That statement simply is simply a comparison of numbers.

EPA has directly provided guidance on how exceedances should be characterized. First, EPA has clearly established that exceeding a reference dose does not signify risk, and that reference values cannot be used to quantify risk. Such a comparison of a concentration to an MCL value is essentially the same as developing a Hazard Quotient value, where EPA and ATSDR are unambiguous in establishing that Hazard Quotient and Hazard Index values do not quantify risk. In that MCL values are ideally based on non-cancer reference dose values, it follows that an exceedance of the MCL value cannot be assumed to represent an increase in risk.

“In general IRIS values [reference doses, reference concentrations, inhalation unit risk values, oral slope values] cannot be validly used to accurately predict the incidence of human disease or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental doses. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposure to a chemical influence the occurrence and extent of human disease.”<sup>82</sup>

MCL values are not quantitatively based on cancer risk. MCL-Goal, or MCL-G values are established for chemicals. The MCL-G value for carcinogens is zero. However, MCL-G values are not enforceable standards; MCL values are enforceable. For carcinogens, the MCL is set as close to zero as feasible, determined largely by the “practical quantitation limit”, which is determined by factors that include technical feasibility (e.g., what is the lowest concentration in water detectable under sophisticated laboratory techniques?) and economic considerations (e.g., how much does a high-powered analytical test cost compared to more routine analytical tests?). Under these considerations, EPA established the MCL values for chemicals like those at Camp Lejeune. EPA has set the MCL for PCE, TCE and benzene at 5 ppb and vinyl chloride at 2 ppb.<sup>83</sup> Using EPA’s upper bound oral slope factor values and assuming a 70 kg person drinks 2 liters of tap water per day for 70 years, the upper bound risks for these contaminants range from 0.3 to 41 excess cancers per million individuals, and the combined upper bound risk estimate is 56 excess cancers per million individuals, both under very conservative, health protective assumptions.

EPA’s practice of interpreting toxicology data and estimating human exposures employs health-conservative measures, and regulatory values, such as MCL values incorporate a compounded level of caution. Using MCL values to maintain the quality and safety of tap water is mandated by the SDWA.

---

<sup>82</sup>Integrated Risk Information System, at: <https://assessments.epa.gov/risk/document/&deid%3D2776#:~:text=In%20general%20IRIS%20values%20cannot,c hemical%20exposures%20have%20on%20humans.>

<sup>83</sup> The MCLs for TCE, vinyl chloride, and benzene were finalized in 1987, effective in 1989 (Fed. Reg 52, 130(1987)). The MCL for PCE was finalized in 1991, effective in 1992 (Fed. Reg. 56, 20(1991)).

However, it's important to note that the Act itself does not explicitly define what constitutes an unreasonable risk to health. (Orme Zavaleta<sup>84</sup>, 1992).

---

<sup>84</sup> Dr Jennifer Orme-Zavaleta was an EPA scientist and manager.

## 12. CHEMICAL MIXTURES AND INTERACTIONS

Several Plaintiffs' Experts, including Drs. Hatten, Bird, Gondek, Felsher, Hu, and DeMiranda, inappropriately assume that the chemicals of interest at Camp Lejeune create a mixture that in which the toxicity is greater than the additive sum of the toxicities of the individual chemicals. For the reasons below, this assumption is unjustified.

A chemical mixture is represented by an exposure whereby the individual is exposed to multiple chemicals. The chemicals may come from the same formulation, as a soft drink, or may come from different sources (e.g., drinking water, canned food, breathing contaminated air). Understanding how a chemical is metabolized (further discussed in Section 12.1.1.) and distributed through the body is a field of study known as pharmacokinetics (also called toxicokinetics). Exposure concentrations in air and water are breathed in and drunk, then the chemicals are absorbed into the blood, and then sent indirectly or directly to the liver for metabolism. The remaining chemical and its metabolites are carried by blood to the tissues and organs.

A chemical's effect is not dependent on the chemical concentration in air or water; the amount of air we breathe or the amount of water we drink; the total amount of the chemical that enters the body through the lungs, skin, or stomach; or the amount that is metabolized. The effect depends on the amount of the active chemical that is present in the tissue where the effect is shown.

Pharmacokinetic evaluations reduce some uncertainty in risk assessment by improving our understanding of the dose response relationship – specifically by moving what we call “dose” close to the biological point in the organ or tissue where the effect is produced.

In a nutshell, pharmacokinetic models can translate the point of departure dose (in units of mg/kg body weight) in animal studies<sup>85</sup> to a tissue concentration in humans, expressed as milligrams of the chemical per liter of liver volume. These models are important because they also account for metabolism of the chemical in the liver and the distribution of both unmetabolized (parent) chemical and chemical metabolites to the tissues. Some of the chemicals of interest for Camp Lejeune are well-enough studied that pharmacokinetic modeling has been applied in their risk assessments.<sup>86</sup> This literature must be taken into consideration when assessing the effect of mixtures.

### 12.1. Not All Mixtures Cause an Interaction that Increases Toxicity

---

<sup>85</sup> If it is known that the chemical is metabolized to become the molecule (the metabolite) that produces toxicity, or whether it is the unmetabolized parent form of the chemical that produces toxicity, then that knowledge is used to program the model to estimate the tissue concentration of the toxic form of the chemical (e.g., mg metabolite per liter liver) to refine the understanding and presentation of dose response relationships, and for use in animal to human extrapolation and the assessment of human variability.

<sup>86</sup> TCE, PCE, and vinyl chloride

The Plaintiffs' Experts inappropriately assume the mixture causes an interaction. "Interaction" is a technical term in risk assessment which ATSDR (2018) defines as "[w]hen the effect of a mixture is different from the expectation of additivity based on the dose-response relationships of the individual components." Interaction means that when an exposure involves two or more chemicals that the effect(s) are not accurately predicted by adding the effects from the individual chemicals together – the end result could be higher or lower than expected.

Saying things like the exposure to an additional chemical "increases the toxicity of the first chemical" is an ambiguous and potentially inaccurate statement. Such a statement alone does not indicate that an interaction has taken place. If the toxicity can also be produced by the second chemical, then the extent to which the toxicity was increased should be determined. The "increased" level of the response may be the result of an interaction, or it might just be the result of adding together the same response produced by each of the two chemicals. This is true for both non-cancer and cancer findings: for these effects that might occur from a mixture, EPA and ATSDR guide the simple addition of the effects of the chemicals and a deeper evaluation if the risk estimate warrants such. The PHA acknowledges that this is what was done in that assessment and that doing so represents a "health-conservative approach."

#### 12.1.1. Metabolism of Chemical Mixtures

Metabolism is an important aspect of single-chemical and chemical mixtures toxicity and risk assessment. Chemicals can cause effects in the "parent" form of the chemical, which is the form taken into the body and not yet metabolized. Chemicals are metabolized in the liver, where the parent chemical is converted to a metabolite which has a different chemical structure and different toxicological properties. The metabolite formed can be more toxic than the parent (this kind of metabolism is the bioactivation type), or the metabolite can be less toxic than the parent (this kind of metabolism is the detoxication kind). Whether metabolism is a bioactivation or a detoxication kind depends on the chemical and the toxicity. For many volatile organic chemicals like PCE, TCE, and vinyl chloride, metabolism is a bioactivation process.

Because the toxicities of many chemicals are understood to be caused by the unmetabolized (parent) chemical or its metabolites, and because of the many ways to study metabolizing enzymes, we can predict whether and under what exposure conditions one chemical might alter the metabolism of another chemical. But, because some of these studies are conducted outside the body and may use chemical doses that cannot be found in the actual human or animal body, these studies show an interaction at the level of metabolism that is unlikely to occur inside the body. For that reason, their results are not pertinent to studying the effect of an exposure to multiple chemicals.

Notably, not all chemical mixtures produce an interaction in risk assessment terms. When one chemical alters the metabolism of another chemical, this is a metabolic interaction. Metabolic interactions are not the same as toxicological interaction or a risk assessment interaction.

Interaction at the level of chemical metabolism is not the same as interaction at the toxicity or risk assessment level.

A metabolic interaction may occur when two chemicals are metabolized by the same enzyme in the liver, as are many volatile organic chemicals including TCE, PCE and vinyl chloride. In a mixture's exposure to chemicals like these, the metabolic capability of the

enzyme is divided between the chemicals. However, if the enzyme's metabolic capability is greater than the demand for metabolism by the combined doses of the chemicals, then a competition between the chemicals for metabolism is unlikely and there will be no metabolic (or toxicologic) interaction. The result is that each chemical will be metabolized as if it is the only chemical present. Conversely, if the combined doses of the chemicals exceed the enzyme's metabolic capacity - based on biochemical parameters - the enzyme will prefer to metabolize one chemical over the other one. In such cases, a competition for metabolism will occur and there may be a metabolic interaction. But because a metabolite might be toxic or non-toxic, the toxicological outcome of the metabolic interaction cannot be known when all that is known is that a metabolic interaction occurred.

Five results are possible when two chemicals are metabolized by the same enzyme and there is a metabolic competition:

- There may be no influence on toxicity;
- The toxicity of the first chemical may be increased;
- The toxicity of the first chemical may be decreased;
- The toxicity of the second chemical may be increased;
- The toxicity of the second chemical may be decreased.

It must not be taken for granted that because there is a metabolic interaction in the liver that toxicity will be increased. The effect may be caused by the unmetabolized parent chemical or by a bioactivated metabolite, and the corollary may be true for other effects caused by the same chemical. If metabolism is altered, it may increase the likelihood of one effect which decreases the likelihood of another effect.

In fact, knowledge of which effects are associated with the parent chemical or a metabolite appears in EPA's Toxicological Review documents for chemicals like TCE and PCE. In ATSDR's Toxicological Profiles and Interaction Profiles for Camp Lejeune chemicals, ATSDR maintains that interactions are unlikely and that the additive approach to assess the risks of these chemicals is appropriate.

None of Plaintiffs' Experts provided justification in assuming an interaction occurred among the chemicals of interest at Camp Lejeune nor did they provide justification that a metabolic competition occurred.

## 12.2. Synergistic Interactions do Not Occur for Camp Lejeune Chemicals

Synergy is defined (EPA, 2000d) as "[w]hen the effect of the combination is greater than that suggested by the component toxic effects."

ATSDR in fact evaluated interactions for some pairs of chemicals of interest at Camp Lejeune chemicals in documents called Interaction Profiles.<sup>87</sup> The PHA has relied on these documents and concluded that the combined effect of chemicals was not increased, and, in some cases, may be decreased. Additionally, ATSDR has developed Interaction Profiles for pairs of chemicals including some Camp Lejeune chemicals,

---

<sup>87</sup> Interaction profiles are listed *en masse* at: <https://www.atsdr.cdc.gov/interaction-profiles/about/index.html>

and respective Toxicological Profile documents for individual chemicals address the likelihood of interactions. To appropriately understand the interaction of chemicals, one should look to these references.

ATSDR has developed a number of Interaction Profiles for chemical mixtures. In developing these Interaction Profiles, ATSDR reviews information on the toxicity of the mixture of interest (typically four or five chemicals per mixture) and data on the single chemicals to develop conclusions of the likelihood of interactions and makes recommendations on what type of mixtures interaction to apply (e.g., less than additive, additive, synergistic) when assessing the risks of the mixture. Five Interaction Profiles include mixtures which contain at least one chemical of concern for Camp Lejeune, including PCE, TCE and vinyl chloride. None of these suggested that synergy be considered for these chemicals.

Specifically, in the Interaction Profile for 1,1,1-Trichloroethane, 1,1-Dichloroethane, Trichloroethylene, and Tetrachloroethylene, ATSDR noted that there was “limited evidence that tetrachloroethylene may inhibit the toxic action of trichloroethylene on liver and kidney.” In other words, PCE may decrease the effect of TCE on the liver and kidney. The PHA, citing this interaction profile, wrote, “[t]here does not appear to be evidence of synergistic effects (i.e., greater than additive) resulting from combined exposures to PCE and TCE.” (ATSDR, 2017a). Additionally, in the Interaction Profile for Chloroform, 1,1-Dichloroethylene, Trichloroethylene and Vinyl Chloride, ATSDR concluded that risks between TCE and vinyl chloride would be additive at low concentrations and would become less than additive at concentrations above 30 ppm. Notably, in the relevant Interaction Profiles, ATSDR never concluded that the Camp Lejeune chemicals of interest were involved in a synergistic, or even greater than additive interaction, as the Plaintiffs’ Experts assume. Summing up the state of knowledge, the PHA concluded that the additive approach (not a synergistic approach) was conservative, using the term “health-protective”, writing, “[i]n summary, given the limited information about the combined effect of these chemicals at the levels at Camp Lejeune, the additive approach used for Cancer Risk and Hazard Index provides a conservative (health-protective) evaluation of exposure and has been incorporated into this [Public Health A]ssessment.” (ATSDR, 2017a).

Additionally, ATSDR’s Toxicological Profile documents specifically address interactions. For PCE, ATSDR (2019b) reported findings from dry cleaning workers indicating that PCE may inhibit the metabolism of TCE. Therefore, in that TCE-associated toxicities associated with metabolites (e.g., neurological, kidney, liver, immunological, reproductive, developmental<sup>88</sup>) would therefore be reduced by concomitant exposure. For TCE, ATSDR (2019a) summarized interactions of TCE with several chemicals unrelated to Camp Lejeune, but also reported findings demonstrating competition for metabolism between vinyl chloride and TCE (Barton et al. 1995). Such a co-exposure to vinyl chloride and TCE would be expected to decrease the TCE metabolite-driven toxicities including neurological, kidney, liver, immunological, reproductive, and developmental systems, as mentioned above for PCE. Barton et al. (1995) determined that competition for metabolism in humans would not occur at concentrations below 10 ppm. Barton et al. (1995) also demonstrated that exposure of rats to 40 ppm (no other concentration was studied) of trans-1,2-dichloroethylene resulted in decreased cytochrome P-450 activity, demonstrated by reduced

---

<sup>88</sup> See Table 5-27 of the Toxicological Review for Trichloroethylene (EPA, 2011a)

(but not eliminated) metabolism of TCE and vinyl chloride in exposed rats. This would decrease the toxicities associated with TCE metabolites. For vinyl chloride, ATSDR (2024) reiterated the findings of Barton et al. (1995), indicating that competition for metabolism between TCE and vinyl chloride would only occur when both chemicals were present at concentrations greater than 10 ppm. Because the toxicity of vinyl chloride is thought to result from a metabolite formed by the enzyme that also metabolizes TCE, reduction of vinyl chloride metabolism by TCE would result in a decreased (liver) toxicity attributed to vinyl chloride. For cis- and trans-1,2-dichloroethylene, ATSDR (2023) did not identify any interactions. For benzene, ATSDR (2007) indicated that consumption of alcohol may increase the hematological effects of benzene.

Despite this literature, the Plaintiffs' Experts (Drs. Hatten, Bird, Gondek, Felsher, Hu, and DeMiranda) inappropriately assume the chemicals of interest at Camp Lejeune can or do interact synergistically. A reference to literature describing a synergistic interaction between cigarette smoking and asbestos exposure on the development of lung cancer is cited by these experts. However, neither these chemicals nor this health effect is the subject of this litigation. Rather, to appropriately understand the interaction of chemicals, one should consider pertinent literature (e.g., Barton et al., 1995), ATSDR's PHA for Camp Lejeune, ATSDR's Interaction Profiles, and ATSDR's Toxicological Profiles for the chemicals at issue, all of which conclude otherwise.

Metabolism is a critical part of understanding how a chemical is processed and distributed through the body, and a place where chemical interactions may alter the formation and distribution of chemical metabolites and unmetabolized parent chemicals. Metabolism is an important mediator of toxicity and many of the toxicities associated with Camp Lejeune chemicals are dependent on chemical metabolites. Interactions resulting in increased toxicity (synergistic interactions; synergy) are mentioned (but not emphasized or substantiated) in the PHA and are maintained as distinct possibilities by the Plaintiffs' Experts. However, the PHA, the Interaction Profiles and the Toxicological Profiles for these chemicals have consistently maintained that an additive approach is valid for these chemicals. ATSDR presents no information that would support a synergistic interaction, and does in fact discuss conditions that would result in a potential metabolic competition with a resulting *decrease* in some toxic effects.

### 13. EPA's Ban of TCE Does Not Apply to Drinking Water Contamination at Camp Lejeune

The Toxic Substances Control Act (TSCA) is within the purview of EPA's Office of Chemical Safety and Pollution Prevention. Under TSCA, EPA is responsible for exposures and risk to workers, occupational non-users, consumers, and bystanders. This program concluded, "After evaluating 54 conditions of use, [EPA's TSCA program] determined that TCE presents an unreasonable risk to human health under its conditions of use based on risk of injury to health of workers, occupational non-users (ONUs), consumers, and bystanders." (EPA, 2022b). Generally speaking, workers' employment activities involve the use of TCE-containing products; occupational non-users are individuals who work in facilities where TCE is used but are not directly involved with TCE-containing products; consumers are those who may use products that contain TCE; and bystanders are those who may be exposed to TCE from products used non-commercially. While drinking water might be considered a "product" outside the context of TSCA, the regulation of contaminants in drinking water is not covered by TSCA, but is instead covered by the Safe Drinking Water Act, administered by EPA's Office of Water. This is directly stated by EPA in the Final Risk Evaluation for Trichloroethylene (EPA, 2020): "EPA excluded ambient air, drinking water, land disposal, ambient water, and waste incineration pathways leading to exposures to the general population and terrestrial organisms from Risk Evaluation since those pathways are under the jurisdiction of other environmental statutes administered by EPA."

Under TSCA, for TCE EPA has identified 54 conditions of use. The conditions did not include use of drinking water contaminated with TCE. TSCA uses its own peer reviewed methodology to estimate inhalation and dermal (but not oral) exposures to the above-named groups of people, for the identified Conditions of Use. These exposures were compared to a risk assessment point of departure value for autoimmunity in mice developed from the study by Keil et al. (2009).<sup>89</sup> The margin of exposure was determined as the ratio of the exposure to the thrice-extrapolated study point of departure to an HED99<sup>90</sup> value for TCE. But, instead of using the true point of departure represented by the dose of TCE that mice consumed, TSCA extrapolated this oral dose as many as four times to get to a point of departure value used in exposure comparisons.

The number and type of extrapolations necessary depends on the characteristics of the underlying study. If the underlying study was conducted in animals or humans exposed for short periods during the day, the first extrapolation would "average out" the concentration over the course of a day (performing the duration adjustment, see Section 8.9). A second extrapolation may be necessary for some studies. If the underlying study was by the oral route and an inhalation risk value were being developed (or vice versa), an extrapolation across routes would be required, whether the underlying study was in animals or

---

<sup>89</sup> In the Final Risk Evaluation for Trichloroethylene, in describing the impact of effect severity, EPA (2020) wrote, "[i]n contrast, the POD for autoimmunity from (Keil et al., 2009) is an example of a POD based on an early biomarker that may not be adverse itself."

<sup>90</sup> HED99 is the point of departure extrapolated from the animal point of departure to Human Equivalent Dose (or Concentration) expressed in persons more sensitive than 99% of the human population.

humans. If the underlying study was conducted in animals, extrapolation from the animal species to the generally representative human would be necessary. And whether the underlying study was conducted in animals or humans, if it does not represent findings from humans considered the most sensitive, then an extrapolation from the general human to the most sensitive human would be necessary. When estimated exposures are compared to point of departure values, it is imperative to understand that the HEC99 or HED99 values do not represent the point of departure values in the underlying study, regardless of whether that study was conducted in animals or humans, unless it can be verified that the study was performed using humans considered to be the most sensitive.

Using physiologically based pharmacokinetic models for TCE, TSCA first extrapolated the point of departure from an oral dose in mice to an inhalation concentration for mice, then extrapolated that inhalation concentration from mice to an inhalation concentration that the average human would be exposed to, and finally extrapolated that to a concentration that would be expected to produce the same dose in a human more sensitive than 99% of the human population. This, health protective and conservative extrapolated point of departure, not the animal point of departure, is the value that TSCA compared to conservative estimates of exposure for the identified conditions of use, which did not include use of drinking water with environmental levels of TCE contamination.

Inhalation exposures were conservatively estimated for 54 conditions of use and compared to the extrapolated point of departure as identified above. For consumers not occupationally exposed, EPA (2020, Table 5-27) identified eight categories of use and 25 products in sub-categories for any condition of use, for any exposure group. Again, TCE-contaminated drinking water was not identified as a use category or product. TSCA did not estimate an inhalation or dermal exposure to TCE from drinking water. Based on the comparison of estimated exposure to the extrapolated point of departure, under TSCA, EPA determined that an unreasonable risk was demonstrated for 52 of the 54 conditions of use. However, under TSCA, EPA does not make an overall decision of unacceptable risk based on findings of unreasonable risk for any specific condition of use, but considers that findings for individual conditions of use may support a finding of unreasonable risk – which for TCE resulted in the ban of TCE. While it may be inviting to compare the levels of exposure estimated in the TSCA risk assessment to exposure estimates developed for Camp Lejeune exposures, the use of different methods in the respective evaluations limits the conclusions that can be drawn from such a comparison. The conditions of use evaluated through TSCA may result in substantially higher exposures to TCE than exposures from what may have been present in the Camp Lejeune drinking water. The determinations of unreasonable risk from a condition of use for variously exposed populations figured into the overall determination of an unreasonable risk for TCE. For some populations and for some conditions of use, worst case assumptions, including instances where industrial hygiene practices were violated, likely impacted conclusions of risk reached by TSCA. For example, it was assumed in some cases that workers failed to wear the required personal protective equipment.

For reasons including those identified above, the TSCA evaluation of TCE and the resulting EPA ban on TCE does not address the potential risk from exposures to TCE via contaminated drinking water, including those at Camp Lejeune.

## 14. CONCLUSION

I have reached the opinions stated in this report to a reasonable degree of scientific certainty, and reserve the right to modify them or include other opinions on the basis of additional information

Risk assessment is an iterative process that begins with a screening effort using biased values for both exposure and risk that, when combined produce an overly biased theoretical upper bound estimate of risk. The purpose of risk screening exercises like that in ATSDR's PHA is to screen out the possibility of risk. However, when screening risk assessments fail to eliminate the possibility that risks might be elevated, additional investigation is required. The potential risks indicated in the PHA and in Rosenfeld et al. (2024) have not yet been carefully evaluated according to the guidance issued by EPA or ATSDR.

When the screening-level risk assessment results cannot screen out the possibility of risk, several important issues should be evaluated through a Risk Characterization process. This should consider that risk values like Reference Dose, Reference Concentration, and Minimal Risk Level values are each conservative, health-protective and embody a margin of safety. EPA and ATSDR have clearly stated that exceedance of their non-cancer values does not imply risk - that these values cannot be used to quantify risk. That caveat extends to other values that are based on Reference Dose, Reference Concentration and Minimal Risk Level values, as well.

Moreover, Hazard Quotient and Hazard Index values greater than 1 indicate a level of concern and identify chemicals or sites that should be further evaluated, but there is no numerical value that connotes risk or causality. Adding together the Hazard Quotients for a given organ in the Target Organ Toxicity Dose approach without confirmation that their modes of action are similar, as done in PHA, represents a conservative health protective assumption. Additionally, ATSDR has concluded that the additivity approach represents a health conservative approach and that a synergistic interaction among these chemicals is unlikely.

Regardless of their basis, presentations of point estimates of risk should be accompanied by an explanation. The uncertainties, assumptions and extrapolations included in both risk values and estimates of exposure should be identified and discussed in a Risk Characterization process, which has not yet been presented for Camp Lejeune. Such a process would address, among other things, the effect that serves as the basis of the risk value used and describe whether it represents a biologically meaningful event or just a statistically-significant finding. The Risk Characterization should ensure that the assessment's conclusions are developed within the Scope of the risk assessment – that the results are interpreted within the purpose for which the assessment was undertaken. And, in the case of the Public Health Assessment and the manuscript by Rosenfeld et al. (2024) the purposes were respectively, to determine whether a closer look should be taken and to demonstrate proof of concept for a specific approach for cancer risk estimation for Camp Lejeune.

The evaluation of cancer risk is also conservative, health-protective. Some slope factors like that for kidney cancer in the IRIS assessment for trichloroethylene may be based on findings in humans occupationally exposed to high concentrations in the workplace. Using a mode of action that is assumed at high doses to assess the risks of lower exposures represents the assumption that the mode of action is operative at lower doses. The kidney cancer associated with trichloroethylene exposure has been characterized as a high-dose effect, and EPA (2011a) recognizes this extrapolation from high occupational

exposures to lower environmental exposures as a “major uncertainty” in its cancer risk assessment for trichloroethylene.

Maximum Contaminant Level values are enforceable standards and regulatory (not risk) values developed for chemicals on the basis of health conservative assumptions. These values are designed with the objective of mitigating potential risk to populations, rather than addressing the likelihood of risk resulting from an excess exposure to any individual. The risk of drinking water concentrations cannot be quantified by comparison to Maximum Contaminant Level values.

Finally, EPA’s Office of Chemical Safety and Pollution Prevention, TSCA decision to ban TCE is not based upon environmental contamination of drinking water. This conclusion was reached by examining 54 individual conditions of use – which did not include drinking water - for which the TSCA Program developed unique and conservative exposure estimates. The decision is not related to the health risks from such contamination, but is from a conservative extrapolated risk from other uses of TCE. Thus, the decision to ban TCE is not pertinent to the TCE exposures possible at Camp Lejeune.

## 15. REFERENCES

This also includes references listed on my CV and those referenced in the Report.

Adamson A, Ilieva N, Stone WJ, De Miranda BR. (2023). Low-dose inhalation Exposure to trichloroethylene induces dopaminergic neurodegeneration in rodents. *Toxicol Sci* 196:218-228.

ATSDR. (1993). Agency for Toxic Substances and Disease Registry. Cancer policy framework. Atlanta: US Department of Health and Human Services. January 1993. Available at: <http://www.atsdr.cdc.gov/cancer.html>

ATSDR. (1997). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Trichloroethylene

ATSDR. (2004) Agency for Toxic Substances and Disease Registry. Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology, May, 2004

ATSDR. (2005). Agency for Toxic Substances and Disease Registry. Public Health Assessment Guidance Manual (update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, January, 2005.

ATSDR. (2006). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Vinyl Chloride

ATSDR. (2007). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Benzene

ATSDR. (2017a). Agency for Toxic Substances and Disease Registry. Public Health Assessment Camp Lejeune Drinking Water, U.S. Marine Corps Base Camp Lejeune, North Carolina, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, January 20, 2017.

ATSDR. (2017b). Agency for Toxic Substances and Disease Registry. ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, January 13, 2017.

ATSDR. (2018). Agency for Toxic Substances and Disease Registry. Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Toxicology Division, Atlanta, Georgia. February, 2018.

ATSDR. (2019a). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Trichloroethylene.

ATSDR. (2019b). Agency for Toxic Substances and Disease Registry. Toxicological Profile for tetrachloroethylene.

ATSDR. (2023). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Dichloroethylene.

ATSDR. (2024). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Vinyl Chloride.

Barnes DG, Dourson M. (1988). Reference dose (RfD): description and use in health risk assessment. *Regulatory Toxicology and Pharmacology*, 8, 471–486.

Barton HA, Creech JR, Godin CS, Randall GM, Sekel CS. (1995). Chloroethylene mixtures: Pharmacokinetic Modeling and in vitro Metabolism of Vinyl Chloride, Trichloroethylene, and trans-1,2-Dichloroethylene in Rat. *Toxicol Appl Pharmacol* 130:237-247.

Beck BD, Conolly RB, Dourson ML, Guth D, Hattis D, Kimmel C, Lewis SC. Symposium Overview: Improvements in Quantitative Non-cancer Risk Assessment. *Fundam Appl Toxicol* 20:1-14, 1993.

Bogen KT. (2005) Risk Analysis for Environmental Health Triage. *Risk Anal* 25:1085-1095.

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers S, Willcocks D, Farland W. IPCS Framework for analyzing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology* 36:781-792, 2006.

Boobis, AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C. 2008. "IPCS Framework for Analyzing the Relevance of a Non-cancer Mode of Action for Humans." *Critical Reviews in Toxicology* 38 (2): 87–96.

Bove, FJ. 2024. " Evaluation of cancer incidence among Marines and Navy personnel and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune (Preprint)." doi: 10.1101/2024.01.27.24301873

Bus J. The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21<sup>st</sup> century toxicology paradigm. *Current Opinion in Toxicology* 3:87-91, 2017.

Charbotel, B; Fevotte, J; Hours, M; Martin, J-L; Bergeret, A. (2006). Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. *Ann Occup Hyg* 50: 777-787. <http://dx.doi.org/10.1093/annhyg/mel039>.

Conolly RP, Clewell HJ, Moore MM, Campbell JL, Cheng W, Gentry PR. PBPK modeling to evaluate maximum tolerated doses: A case study with 3-chloroallyl alcohol. *Frontiers in Pharmacology* Feb 22 2023. Doi10.3398/fphar.2023.1088011

CRARM, Commission on Risk Assessment and Risk Management. (1997) Risk Assessment and Risk Management in Regulatory Decision-Making, Final Report Volume 2, Washington, DC.

DeWoskin RS, Lipscomb JC, Thompson C. (2007). Pharmacokinetic and Physiologically Based Pharmacokinetic Models in IRIS assessments. In: Lipscomb JC and Ohanian EV (eds), *Toxicokinetics and Risk Assessment*. Informa Healthcare Publishers, New York, NY.

Dourson ML, Stara JF. (1983). Regulatory history and experimental support of uncertainty (safety) factors. *Regulatory Toxicology and Pharmacology*, 3, 224–238.

EPA. (1986a). U.S. Environmental Protection Agency. Guidelines for the Health Risk Assessment of Chemical Mixtures. *Federal Register*, 185(51), 34014–34025.

EPA (1986b). U.S. Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington DC. EPA/630/R-00/004, September 1986.

EPA. (1989). U.S. Environmental Protection Agency. Risk Assessment Guidance for Superfund. Volume I. Human Health Evaluation Manual. Part A. (Interim Final) (EPA/540/1-89/002; PB90-155581). U.S. Environmental Protection Agency. Office of Solid Waste and Emergency Response.

EPA (1991). U.S. Environmental Protection Agency). Guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826. <http://www.epa.gov/iris/backgr-d.htm>

EPA (1987). "National Primary Drinking Water Regulations: Synthetic organic chemicals; Monitoring for unregulated contaminants (Final)." *Fed. Reg.* 52(130):25690-25717. July 8. [https://archives.federalregister.gov/issue\\_slice/1987/7/8/25685-25734.pdf#page=6](https://archives.federalregister.gov/issue_slice/1987/7/8/25685-25734.pdf#page=6)

EPA (1991a). "National Primary Drinking Water Regulations: Final Rule (40 CFR Parts 141, 142 & 143). National Primary Drinking Water Regulations: Proposed Rule (40 CFR Parts 141 & 142)." *Fed. Reg.* 56(20):3526-3614. January 30. [https://archives.federalregister.gov/issue\\_slice/1991/1/30/3521-3597.pdf#page=6](https://archives.federalregister.gov/issue_slice/1991/1/30/3521-3597.pdf#page=6)

EPA (1991b). U.S. Environmental Protection Agency. OSWER Directive 9355.0-30, Role of the Baseline Risk Assessment in Superfund Remedy Selection Decisions. Office of Solid Waste and Emergency Response. US Environmental Protection Agency, Washington, D.C. April 22, 1991.

EPA (1992). U.S. Environmental Protection Agency. Guidance on Risk Characterization for Risk Managers and Risk Assessors. Memo, Feb 26, 1992, from F. Henry Habicht to Assistant Administrators and Regional Administrators.

EPA (1994). U.S. Environmental Protection Agency. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Research Triangle Park, North Carolina EPA/600/8-90/066F, October, 1994.

EPA (1995). Environmental Protection Agency. Guidance for Risk Characterization. Science Policy Council, February, 1995. <https://www.epa.gov/sites/default/files/2015-11/documents/guidance-risk-characterizationfeb1995.pdf>

EPA (1996). U.S. Environmental Protection Agency. Guidelines for reproductive toxicity risk assessment [EPA Report] (pp. 1-143). (EPA/630/R-96/009). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. [https://www.epa.gov/sites/production/files/2014-11/documents/guidelines\\_repro\\_toxicity.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf)

EPA (1998). U.S. Environmental Protection Agency. Guidelines for neurotoxicity risk assessment [EPA Report] (pp. 1-89). (EPA/630/R-95/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment>

EPA. (1999). Environmental Protection Agency. Extrapolation of Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure. IRIS Assessment and Supporting Documents for Benzene. EPA.gov/IRIS.

EPA (2000a). Environmental Protection Agency. IRIS Assessment and supporting documents for Vinyl chloride. EPA.gov/iris

EPA. (2000b). Environmental Protection Agency. IRIS Chemical Assessment Summary for Benzene, updated 4/17/2003. EPA.gov/IRIS

EPA. (2000c). Environmental Protection Agency. Risk Characterization Handbook (EPA/100/B-00/002). Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency. W:\Reference\_Materials\Risk Assessment Tools\USEPA Risk Characterization Handbook\Risk Characterization Handbook 2000.pdf

EPA (2000d). Environmental Protection Agency. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum, Washington, DC. EPA/630/R-00/002, August, 2000.

EPA (2002a). Environmental Protection Agency. Toxicological Review for Benzene in IRIS Assessment for Benzene. EPA.gov/IRIS

EPA (2002b) Environmental Protection Agency. A Review of the Reference Dose and Reference Concentration Process. Risk Assessment Forum, Washington DC. EPA/630/P-02/002F, December, 2002.

EPA. (2003). Environmental Protection Agency. Draft final guidelines for carcinogen risk assessment final (external review draft). U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, NCEA-F0644A. March 2003.

EPA. (2004). Environmental Protection Agency. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual Part E, Supplemental Guidance for Dermal Risk Assessment. Office of Solid Waste and Emergency Response, Office of Superfund Remediation and Technology Innovation U.S. Environmental Protection Agency Washington, DC. EPA/540/R/99/005, July, 2004.

EPA (2005). Environmental Protection Agency. Guidelines for Carcinogen risk assessment. U.S. Environmental Protection Agency, EPA/630/P-03/001B. March, 2005.

EPA (2006). U.S. Environmental Protection Agency. Approaches for the Application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment. EPA/600/R-05/043F, National Center for Environmental Assessment, Washington, D.C.

EPA (2010a). Environmental Protection Agency. IRIS Assessment and supporting documents for cis-1,2-dichloroethylene. EPA.gov/iris

EPA (2010b). Environmental Protection Agency. IRIS Assessment and supporting documents for trans-1,2-dichloroethylene. EPA.gov/iris

US EPA (2011a). Environmental Protection Agency. IRIS Assessment and supporting documents for Trichloroethylene. EPA.gov/iris

US EPA (2011b). Environmental Protection Agency. Final Recommended Use of Body Weight<sup>3/4</sup> as the Default Method in Derivation of the Oral Reference Dose. U.S. Environmental Protection Agency, Office of the Science Advisor, Risk Assessment Forum, Washington, DC. EPA/100/R11/0001

EPA (2011c) Environmental Protection Agency. Exposure Factors Handbook 2011 Edition (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011.

EPA (2012a). Environmental Protection Agency. Benchmark dose technical guidance. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/100/R-12/110, June, 2012.

EPA (2012b). Environmental Protection Agency. Toxicological Review for Tetrachloroethylene. EPA/635/R-08/011F February 2012.

EPA (2012c). Environmental Protection Agency. IRIS Summary for Tetrachloroethylene. EPA.gov/IRIS.

EPA (2014a). Environmental Protection Agency. Framework for human health risk assessment to inform decision Making. U.S. Environmental Protection Agency, Office of the Science Advisor, Risk Assessment Forum. EPA/100/R-14/001, April, 2014.

EPA. (2014b). Environmental Protection Agency. Guidance for Applying Quantitative Data to Develop Data Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Final. EPA/R-14/002F. <http://www2.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf>

EPA (2018). Environmental Protection Agency. 2018 Edition of the Drinking Water Standards and Health Advisories Table. EPA 822-F-18-001, Office of Water, U.S. Environmental Protection Agency, Washington, DC, March 2018.

EPA. (2020). Environmental Protection Agency. Risk Evaluation for Trichloroethylene (No. 740R18008). U. S. Environmental Protection Agency.

EPA. (2021). Environmental Protection Agency. Title 40 – Protection of Environment, Chapter I – Environmental Protection Agency, Subchapter J – Superfund Emergency Planning, and Community Right-to-Know Programs, Part 300 – National Oil and Hazardous Substances Pollution Contingency Plan. Washington, DC.

EPA. (2022). Environmental Protection Agency. Trichloroethylene Unreasonable Risk Determination. [https://www.epa.gov/system/files/documents/2023-01/TCE\\_Final%20Revised%20RD\\_12-21-22-FINAL-v2.pdf](https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf)

EPA (2022a). Environmental Protection Agency. ORD Staff Handbook for Developing IRIS Assessments. U.S. Environmental Protection Agency, Office of Research and Development. EPA 600/R-22/268. December 2022.

EPA. Environmental Protection Agency. (2022b). Non-Technical Summary of the Risk Evaluation for Trichloroethylene, CASRN: 79-01-6. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention, Washington, D.C. EPA Document #740-S-22-005.

EPA. Environmental Protection Agency (2023). Advances in Dose Addition for Chemical Mixtures: A White Paper. Environmental Protection Agency, Risk Assessment Forum, Cumulative Risk Assessment Technical Panel, Washington, D.C. EPA/100/R23/001.

Federal Register 54:22061-22160 (1989).

Federal Register 50:46879-46933(1989).

Federal Register 52, 130 (1987).

Federal Register 56, 20 (1991).

Gaylor DW. (2000). The use of Haber's Law in standard setting and risk assessment. *Toxicology* 14:17-19. DOI 10.1016/s0300-483x(00)00228-6

IPCS (2005). International Programme on Chemical Safety. Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment. (Harmonization Project Document No. 2). Geneva, Switzerland: World Health Organization.  
<http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf>

IPCS (2010). International Programme on Chemical Safety. Characterization and application of physiologically based pharmacokinetic models in risk assessment. (Harmonization Project Document No 9). Geneva, Switzerland: World Health Organization.  
<http://www.inchem.org/documents/harmproj/harmproj/harmproj9.pdf>

Holman E, Francis R, Gray G. (2017a) Part I – Comparing Non-cancer Chronic Human Health Reference Values: An Analysis of Science Policy Choices. *Risk Anal* 37:861-878

Holman E, Francis R, Gray G. (2017b). Part II – Quantitative Evaluation Choices of Choices Used in Setting Non-cancer Chronic Human Health Reference Values Across Organizations. *Risk Anal* 37:879-892.

Kadry AM, Skowronski GA, Abdel-Rahman MS. (1995). Evaluation of the use of uncertainty factors in deriving RfDs for some chlorinated compounds. *J Toxicol Environ Health* 45:83-95.

Keil DE, Peden-Adams MM, Wallace S, Ruiz P, Gilkerson GS. (2009). Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease, *Journal of Environmental Science and Health Part A*, 44:443-453.

Lewis SC, Lynch JR, Nikiforov AI. A New Approach to deriving community exposure guidelines from “No-Observed-Adverse-Effect Levels”. *Regul Toxicol Pharmacol* 11:314-330, 1990

Lilly PD, Simmons JE, Pegram RA. Effect of subchronic corn oil gavage on the acute toxicity of orally administered bromodichloromethane *Tox Lett* 87:93-102, 1996.

Lipscomb JC. (2019). Purpose Driven Risk Assessment. *Toxicol Pathol* 47:1027-1034, 2019.

Lipscomb, JC. (2004). Evaluating the Relationship between Variance in Enzyme Expression and Toxicant Concentration in Health Risk Assessment. *Human Ecol Risk Asses.* 10:39-55.

Lipscomb, JC. (2003). How Differences in Enzyme Expression Can Translate into Pharmacokinetic Variance and Susceptibility to Risk. *J. Child. Health* 1:189-202.

Lipscomb, JC. (2019). Purpose driven risk assessment. *Toxicol Pathol* 47:1027-1034.

Lipscomb, JC. (2021). American College of Toxicology. Special Topics in Toxicology, eLearning Virtual Seminar, Thresholds and Their Derivation. April 22, 2021.

Lipscomb, JC, Garrett, CM, and Snawder, JE. (1997). Cytochrome P450-dependent Metabolism of Trichloroethylene: Interindividual Differences in Humans. *Toxicol Appl Pharmacol*, 142:311-318.

Lipscomb, JC, Fisher, JW, Confer, PD and Byczkowski, JZ. (1998a). In Vitro to in Vivo Extrapolation for Trichloroethylene Metabolism in Humans. *Toxicol Appl Pharmacol* 152:376-387.

Lipscomb, JC, Garrett, CM and Snawder, JE. (1998b). Use of Kinetic and Mechanistic Data in Species Extrapolation of Bioactivation: Cytochrome P-450 Dependent Trichloroethylene Metabolism at Occupationally Relevant Concentrations. *J Occup Health* 40:110-117.

Lipscomb, JC, Teuschler, LK, Swartout, J, Popken, D, Cox, T and Kedderis, GL. (2003a). The Impact of Cytochrome P450 2E1-dependent Metabolic Variance on a Risk Relevant Pharmacokinetic Outcome in Humans. *Risk Analysis* 23:1221-1238.

Lipscomb, JC, Teuschler, LK, Swartout, JC, Striley, CAF and Snawder, JE. (2003b). Variance of Microsomal Protein and Cytochrome P450 2E1 and 3A Forms in Adult Human Liver. *Toxicol Mech Methods*. 13:45-51.

Lipscomb, JC, Lambert, JC and Teuschler, LK. *Chemical Mixtures and Cumulative Risk Assessment*, 253-281. in: *Principles and Practice of Mixtures Toxicology* (M. Mumtaz., ed.), Wiley, 2010.

Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE. (2003). A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action. *Crit Rev Toxicol* 33:591-653.

Mumtaz MM, Poirier KA, Colman J. (1997). The risk assessment of chemical mixtures: Fine tuning the hazard index approach. *J Clean Technol., Environ Toxicol & Occup Med*. 6:189-204.

NRC. National Research Council. (1983). *Risk Assessment in the Federal Government: Managing the Process*. <https://doi.org/10.17226/366>

NRC. National Research Council. (1994). *Science and judgment in risk assessment*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/2125>.

NRC. National Research Council. (2006). *Assessing the human health risks of trichloroethylene: Key scientific issues*. Washington, D.C. National Academies Press.

NRC. National Research Council. (2007a). *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/11970>.

NRC. National Research Council. 2008. *Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/12018>.

NRC, National Research Council. (2009a). *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/12209>.

National Research Council. (2009b). *Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/12618>.

Orme-Zavaleta J. (1992). Toxicological basis for drinking water: Unreasonable risk to health values. *J American College of Toxicology* 11:325-329.

Slikker W, Jr, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, David RM, Doerrner NG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Setzer RW, Swenberg, JA, Wallace K. (2004). Dose-dependent transitions in mechanisms of toxicity. *Toxicol Appl Pharmacol* 201:203-225.

Sonich-Mullin C, Fielder R, Wiltse J, Baetke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice JM, Younes M. (2001). IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis. *Regul Toxicol Pharmacol* 34:146-152.

Stermer AR, Klein D, Wilson SK, Dalajamts C, Baia CY, Hall SJ, Madnick S, Bianchi E, Chiu WA, Boekelheide K. (2019). Differential toxicity of water versus gavage exposure to trichloroethylene in rats. *Environ Toxicol Pharmacol*. 2019 May ; 68: 1–3. doi:10.1016/j.etap.2019.02.003.

Swartout JC, Price PS, Dourson ML, Carlson-Lynch HL, Keenen RE. (1998). A Probabilistic Framework for the Reference Dose (Probabilistic RfD). *Risk Analysis* 18:271-282.

Teuschler LK, Dourson ML, Stiteler WM, McClure P, Tully H. (1999). Health risk above the reference dose for multiple chemicals. *Regul Toxicol Pharmacol* 30:S19-S26,.

Thompson, CM, Sonawane, B, Barton, HA, Dewoskin, RS, Lipscomb, JC, Chiu, WA, and Krishnan, KK. (2008). Approaches for Applications of Physiologically Based Pharmacokinetic Models in Risk Assessment. *J Toxicol Environ Health* 11:1-29.

US CEQ. (1989) U.S. Council on Environmental Quality. Risk Analysis: A guide to principles and methods for analyzing health and Environmental Risks. Executive Office of the President of the United States.

Bringmann G. et al. (1999) Identification of the dopaminergic neurotoxic 1-trichloromethyl-1,2,3,4-tetrahydro-B-carboline in human blood after intake of the hypnotic chloral hydrate. *Anal Biochem* 270:167-175.

Cavalleri A. et al. (1994). Perchloroethylene exposure can induce colour vision loss. *Neuroscience Lett* 179 :162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. *Arch Environ Health* 53:196-198.

Echeverria D. et al. (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects. *JOEM* 37:667-680.

EPA (2004). Environmental Protection Agency. Risk Assessment principles and practices. Office of the Science Advisor Staff Paper. An examination of EPA risk assessment principles and practices. EPA/100/B-04-0001, March, 2004. U.S. Environmental Protection Agency, Washington, D.C.

Gargas ML et al. (1989). Partition coefficients of low-molecular weight volatile chemicals in various liquids and tissues. *Toxicol Appl Pharmacol* 98:87-99.

Gash D.M. et al. (2008). Trichloroethylene : Parkinsonism and Complex I mitochondrial neurotoxicity. *Ann Neurol* 2008;63:184–192.

Keane PC et al. (2019). Trichloroethylene and its metabolite TaClo lead to degeneration of substantia nigra dopaminergic neurons: Effects in wild type and human A30P mutant alpha-synuclein mice. *Neuroscience Lett* 711:134437.

NCI (National Cancer Institute). (1977). Bioassay of tetrachloroethylene for possible carcinogenicity. (NCI-CGTR-13; DHEW Publication No. (NIH) 77-813). Bethesda, Md: National Institutes of Health.

JISA (Japan Industrial Safety Association). (1993). Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice. Hadano, Japan.

Expert Report of Remy J.-C Hennet, December 9, 2024.

Expert Report of Alexandros Spiliotopoulos, December 9, 2024.

Expert Report of Jay L. Brigham, December 9, 2024,

Expert Report of Jay L. Brigham, February 7, 2025.

Expert Report of Ari Kelman, February 7, 2025.

Expert Report of Peter G. Shields, February 7, 2025.

Expert Report on Bladder Cancer of Michael J. McCabe, February 7, 2025.

Expert Report on Kidney Cancer of Michael J. McCabe, February 7, 2025.

Expert Report on Non-Hodgkin's Lymphoma and Leukemia of Michael J. McCabe, February 7, 2025.

Expert Report on Bladder Cancer of Julie E. Goodman, February 7, 2025.

Expert Report on Kidney Cancer of Julie E. Goodman, February 7, 2025.

Expert Report on Non-Hodgkin's Lymphoma of Julie E. Goodman, February 7, 2025.

Expert Report on Leukemia of Julie E. Goodman, February 7, 2025.

Expert Report on Parkinson's Disease of Julie E. Goodman, February 7, 2025.

Expert Report of Morris L. Maslia, October 25, 2024.

Expert Report of Mustafa M. Aral, October 25, 2024.

Expert Report of Norman L. Jones and R. Jeffery Davis, October 25, 2024.

Rebuttal Expert Report of Leonard F. Konikow, January 14, 2025.

Rebuttal Expert Report of Kyle Longley, January 14, 2025.

Rebuttal Expert Report of David Sabatini, January 14, 2025.

Rebuttal Expert Report of Norman L. Jones and R. Jeffery Davis, January 14, 2025.

Rebuttal Expert Report of Morris L. Maslia, January 14, 2025.

Expert Report on Kidney Cancer of Dr. Steven B. Bird, December 5, 2024.

Expert Report on Kidney Cancer of Dr. Michael D. Freeman, December 5, 2024.

Expert Report on Kidney Cancer of Dr. Kathleen M. Gilbert, December 5, 2024.

Expert Report on Kidney Cancer of Dr. Benjamin Hatten, December 5, 2024.

Expert Report on Kidney Cancer of Dr. Timothy Mallon, December 5, 2024.

Expert Report on Bladder Cancer of Dr. Steven B. Bird, December 5, 2024.

Expert Report on Bladder Cancer of Dr. Stephen H. Culp, December 5, 2024.

Expert Report on Bladder Cancer of Dr. Kathleen Gilbert, December 5, 2024.

Expert Report on Bladder Cancer of Dr. Benjamin Hatten, December 5, 2024.

Expert Report on Bladder Cancer of Dr. Laura Plunkett, December 5, 2024.

Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Steven B. Bird, December 5, 2024.

Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Dean W. Felsher, December 5, 2024.

Expert Report on Leukemia and Non-Hodgkin Lymphoma of Dr. Kathleen Gilbert, December 5, 2024.

Expert Report on Leukemia of Dr. Lukasz P. Gondek, December 5, 2024.

Expert Report on Leukemia of Dr. Timothy M. Mallon, December 5, 2024.

Expert Report on Non-Hodgkin Lymphoma of Dr. Howard Hu, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Steven B. Bird, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Amelia K. Boehme, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Jason Cannon, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Lucio Costa, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Briana DeMiranda, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Michael Freeman, December 5, 2024.

Expert Report on Parkinson's Disease of Dr. Gary Miller, December 5, 2024.

Expert Report of Kyle Longley, December 5, 2024.

Supplemental Report of Dr. Jason Cannon, January 10, 2025.

Supplemental Report of Dr. Howard Hu, January 31, 2025.

Supplemental Report of Dr. Steven B. Bird, February 5, 2025.

Bove, FJ. "Videotaped & videoconferenced deposition of Dr. Frank J. Bove [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, October 17, 18, 2024.

Savitz, DA. "Videotaped & videoconferenced deposition of Dr. David A. Savitz [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, June 10, July 17, 2024.

Maslia, M. "Videotaped & videoconferenced deposition of Morris Maslia [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, September 26, 2024.

Martel, SNJ. "Videotaped & videoconferenced deposition of Susan N.J. Martel [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-00897, September 26, 2024.

Agency for Toxic Substances and Disease Registry (ATSDR). 2007b. "Analyses of Groundwater Flow, Contaminant Fate and Transport, and Distribution of Drinking Water at Tarawa Terrace and Vicinity, U.S. Marine Corps Base Camp Lejeune, North Carolina: Historical Reconstruction and Present-Day Conditions: Chapter A." July 2007.

Agency for Toxic Substances and Disease Registry (ATSDR). 2013. "Analyses and Historical Reconstruction of Groundwater Flow, Contaminant Fate and Transport, and Distribution of Drinking Water Within the Service Areas of the Hadnot Point and Holcomb Boulevard Water Treatment Plants and Vicinities, U.S. Marine Corps Base Camp Lejeune, North Carolina: Chapter A." May 2013.

Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC. 2014a. "Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study." Environ. Health 13:68. doi: 10.1186/1476-069X-13-68.

Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC. 2014b. "Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study." Environ. Health 13:10. doi:10.1186/1476-069X-13-10.

Agency for Toxic Substances and Disease Registry (ATSDR). 2018b. "Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune." April 2018.

Bove, FJ; Greek, A; Gatiba, R; Boehm, RC; Mohnsen, MM. 2024b. "Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC base Camp Lejeune: A cohort study." Environ. Health 23(1):61. doi: 10.1186/s12940-024-01099-7.

Bove, FJ. 2024c. "Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: A cohort study." Res. Square doi: 10.21203/rs.3.rs-4171975/v1.

Bove, FJ; Greek A; Gatiba, R; Kohler, B; Sherman, R; Shin, GT; Bernstein, A. 2024d. "Cancer incidence among Marines and Navy personnel and civilian workers exposed to industrial solvents in drinking water

at US Marine Corps Base Camp Lejeune: A cohort study." *Environ. Health Perspect.* 132(10):107008. doi: 10.1289/EHP14966.

Rosenfeld PE, Spaeth KR, McCarthy SJ, Winter SC, Wilson MS, Hagemann M. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955 to 1987. *Water, Air, & Soil Pollution* 2024; 235: 124.

Rosenfeld PE, Spaeth KR, McCarthy SJ, Winter SC, Wilson MS. Camp Lejeune Marine Cancer Risk Assessment for Exposure to Contaminated Drinking Water From 1955-1987 (PrePrint). <https://ssrn.com/abstract=4329666>.

CLJA\_RosenfeldSubpoena\_0000000001

## 16. APPENDIX A

I am being compensated at the rate of \$375 per hour for my work on this case.

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

**Opal Millman, Eric Powell and Laury Powell v. RTX Corporation**

US District Court, Northern District of Indiana

Case No.1:16-CV-312-HAB

Deposition: January 23 and February 8, 2024

**Sandra Taylor, et al v. Schaeffler Group, USA, INC., et al**

Circuit Court of Jasper County, Missouri

Case No.: 20AO-CC00341

Deposition: August 30 and 31, 2023

**JOHN C. LIPSCOMB, PhD, DABT, ATS**

**Personal**

Born January 19, 1962, Little Rock, AR  
Married to Sherri D. Lipscomb, R.N., M.S., two adult children

Lipscomb and Associates, PLLC  
7501 Glenn Hills Drive  
Sherwood, AR 72120  
(513) 470 0409  
[JohnCharlesLipscomb@gmail.com](mailto:JohnCharlesLipscomb@gmail.com)

And

CTEH, LLC  
5120 Northshore Drive  
North Little Rock, AR 72118  
(501) 804 6005  
[jlipscomb@cteh.com](mailto:jlipscomb@cteh.com)

Dr Lipscomb began his career as a biologist at the National Center for Toxicological Research in Jefferson, Arkansas. He later served as a Captain (research toxicologist) in the U.S. Air Force, where he earned the Air Force Achievement Medal for his pioneering work on the military's first large-scale investigation of human metabolic variability. He completed his federal career as a toxicologist and risk assessor in EPA's National Center for Environmental Assessment and National Homeland Security Research Center in Ohio, where he was a chemical manager for three different risk assessment programs and led the development of EPA guidance for quantitative risk assessment and emergency exposure guidance values. He is Chief Scientist for Lipscomb and Associates, PLLC, a toxicology and risk assessment provider in Sherwood, AR and works part-time at CTEH, LLC where he supports toxicology and risk assessment activities for unanticipated chemical exposures. He has nearly 90 peer-reviewed publication credits. His interests include quantitative risk assessments of single chemicals and chemical mixtures, in vitro to in vivo extrapolation, toxicokinetics and non-default extrapolations of dosimetry among and between species. Dr Lipscomb is a Diplomate of the American Board of Toxicology and Fellow of the Academy of Toxicological Sciences. He serves on the Health Advisory Board for NSF International and on the American Industrial Hygiene Association's Emergency Response Planning Committee. He is past president of the Society for Risk Analysis's Dose Response Specialty Group and Ohio chapter, the Society of Toxicology's Risk Assessment Specialty Section and Ohio Valley regional chapter, as well as the American Board of Toxicology. He serves on the Editorial Board for *Toxicological Sciences* and *Toxicology Reports* and is an Associate Editor for *Toxicology Mechanisms and Methods*. He holds bachelor's and master's degrees in biology from the University of Central Arkansas and a Ph.D. in interdisciplinary toxicology from the University of Arkansas for Medical Sciences and is an adjunct professor of Toxicology in the Department of Pharmacology and Toxicology at the University of Louisville.

## Education/Certification

2008	Fellow, Academy of Toxicological Sciences
1995	Diplomate, American Board of Toxicology
1987 - 1991	Doctor of Philosophy Degree - Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR Advisor: Julian E.A. Leakey Dissertation: The Effect of Trimethyltin on Rat Hepatic Glutathione S-Transferase
1980 - 1986	Master of Science, and Bachelor of Science Degrees - Department of Biology, University of Central Arkansas, Conway, AR Advisor: H. Frederick Dalske Thesis: The Transplacental Pharmacokinetics of Trimethyltin in the Rat
2003	Physiologically Based Pharmacokinetic Modeling (two weeks) Colorado State University
2002	Conflict Resolution Atlanta Justice Center
2001	The Four Roles of Leadership Franklin Covey
2001	The Seven Habits of Highly Effective People Franklin Covey
2000	Supervisory Management Training and Development (Certificate) University of Cincinnati
2000	Building High Performance Teams (Certificate) The Commonwealth Center for High-Performance Organizations, John Pickering
1998	Supervisory Management Certificate Training (30 hours) University of Cincinnati
1998	Facilitator Workshop (Certificate) Xavier University (Ohio)
1998	Leadership Development Certificate Training (Certificate) University of Cincinnati

1996 Squadron Officer School, U.S. Air Force,  
Maxwell-Gunter Air Force Base, AL, distance learning.

### **Professional Experience**

2019 – present Chief Scientist, Lipscomb and Associates, PLLC, Sherwood, AR

Serves as Chief Scientist providing experience and expertise in toxicology and risk assessment to clients interested in evaluating the relationship between exposure and risk. Provides quantitative risk assessment service, advice and products based on 22 years' EPA risk assessment experience. Some areas of expertise include the evaluation of oral and inhalation exposures, advanced dose response assessment, data-derived extrapolation factors, chemical specific adjustment factors, and guidance on the design, development, implementation and interpretation of physiologically based pharmacokinetic models for risk assessment application, based on current EPA and international guidance.

2019 – present Senior Toxicologist, CTEH, LLC, North Little Rock, AR

Serves as Senior Toxicologist providing expert toxicology and risk assessment support to answer questions important to clients interested in protecting the health and safety of individuals potentially exposed to chemicals. Responsible for evaluating the relationship between environmental media concentrations and internal doses of potentially toxic chemicals, and for evaluating dose response relationships for multiple biological effects. Supports the emergency response mission function by identifying pertinent data, ensuring data are of adequate data quality and fit for purpose, and recommending values for emergency exposure guidance. Develops and provides training on toxicology and risk assessment and mentors junior health and safety staff.

2016 – 2019 Toxicologist (2016- 2019, GS 0415/15), U.S. Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, OH

Serves as NHSRC's senior toxicologist and expert chemical risk assessor, ensuring the scientific integrity and management oversight of the critical Provisional Advisory Level program in developing risk assessment documents for environmental contaminants and chemical threat agents of national priority. Responsible for reviewing original scientific publications to ensure the accuracy of their findings and conclusions, and evaluating the recommendations of other experts to develop sound risk estimates to support policy decisions of national importance. Participates in and leads interdisciplinary teams of scientists in evaluating risk of toxic chemicals encountered for brief or intermittent durations in buildings or outdoor environments.

1998 – 2016 Toxicologist (1998-2001, GS-0415/13; 2001-2005, GS-0415/14; 2005-2016 GS-0415/15), U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH

Supports the development of refined risk assessment methods, including evaluation of toxic mechanisms, dose-response assessment, exposure quantification and definition of intrinsic modifiers of toxicity. Interprets absorption, distribution, metabolism, elimination and biological activity data from environmental pollutants. Applies sound scientific judgment to develop human health risk assessments. Authors publications, reviews, methods, guidelines and documents relating the toxicological effects of environmental pollutants through internal and external collaborations. Develops and presents instructional material for human health risk assessment. Serves as contract management officer for extramurally-funded research efforts. Assumes management/leadership roles to facilitate research, product and personnel development.

1992 - Present Adjunct Assistant Professor, Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY (2010 – Present); Adjunct Assistant Professor, School of Public Health and Tropical Medicine, Department of Environmental Health Sciences, Tulane University, New Orleans, LA (2000-2005); Adjunct Assistant Professor, Department of Therapeutics, College of Pharmacy, University of Cincinnati, Cincinnati OH (1998 to 2001); Adjunct Assistant Professor, Department of Biochemistry and Molecular Biology, School of Medicine, Wright State University, Dayton OH (1995-1998); Instructor, Biology Department, Sinclair Community College, Dayton, OH (1992-1993).

Developed syllabi and lectures in Chemistry of Life Processes, Xenobiotic Metabolism, Toxicology and Risk Assessment. Course Director for PHTX 618: Introduction to Health Risk Assessment, University of Louisville, Spring 2015

1991 - 1998 Captain, USAF; Research Toxicologist (1991-1993), and Chief, Metabolism Section (1993-1998), Toxicology Division, Armstrong Laboratory, U. S. Air Force, Wright-Patterson Air Force Base, OH

*1993-1998:* Designed and implemented research projects in the area of xenobiotic metabolism in response to Air Force environmental and occupational health needs. Established, staffed and supervised a research section of three technicians. Determined the enzymological basis for human interindividual and species-dependent differences in bioactivation; identified potential modifiers of toxicity. Directed three research projects and provided toxicology support to other in-house and extramural Air Force programs. Leveraged internal and external research funds for maximal effectiveness. Responsible for assimilating available human exposure and toxicity data to estimate human health risk. Reviewed scientific programs, grant proposals, protocols and manuscripts for publication.

*1991-1993:* Planned, conducted and evaluated research on compounds relevant to Air Force missions.

Acted as consultant on toxicology issues. Coordinated research activities between Air Force, civil service and contract personnel. Instructed and trained technicians. Wrote protocols, reviews and manuscripts for publication, communicated findings at meetings.

1984 - 1991                      Biologist, Developmental Mechanisms Branch, Division of Reproductive and Developmental Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR

Served as principal investigator: planned and conducted toxicology research in the areas of pre-, peri-, and postnatal development related to drug metabolism and pharmacokinetics. Ensured proper laboratory safety and waste disposal. Acted as a member of division-based peer-review panel for protocols, reports and manuscripts. Wrote technical reports, reviews and manuscripts for publication. Delivered presentations at national and international scientific meetings.

### **Awards**

- US Environmental Protection Agency, Time Off Award for Exceptional Service to Emergency Response Exposure Guidance, 2017.
- US Environmental Protection Agency, Cash Award for Exemplary Service while on Detail, July, 2016.
- US Environmental Protection Agency, Cash Award for Provisional Peer Reviewed Toxicity Value support, June, 2016.
- US Environmental Protection Agency, Time Off Award for Data Derived Extrapolation Factors Guidance Document, 2015.
- US Environmental Protection Agency, Scientific and Technological Achievement Award, Metabolism Data for Mechanisms of Hepatosteatorsis, 2015.
- Society of Toxicology, Risk Assessment Specialty Section, 2015 “Top-Ten” best abstract Awards for Risk Assessment (Data Derived Extrapolation Factors).
- Society of Toxicology, Risk Assessment Specialty Section, 2014 The Outstanding published paper for Risk Assessment Applications (Tox Sci 131:360-374, 2013).
- US Environmental Protection Agency, Gold Medal for Contributions to Trichloroethylene IRIS Risk Assessment, 2011.
- US Environmental Protection Agency, Scientific and Technological Achievement Award, Bisphenol A Metabolism, 2011.
- US Environmental Protection Agency, Scientific and Technological Achievement Award, Developing Guidelines for Physiologically Based Pharmacokinetic Modeling for Risk Assessment, 2009.
- US Environmental Protection Agency, Bronze Medal for Methods to Assess Cumulative Risk of Environmental Contaminants, 2008.
- US Environmental Protection Agency, Scientific and Technological Achievement Award, Impacts of Age-Specific Dosimetry on Risk Assessment, 2008
- US Environmental Protection Agency, Scientific and Technological Achievement Award, Metabolism Data for Conazole Risk Assessment, 2008
- US Environmental Protection Agency, Bronze Medal for Methods to Evaluate Cumulative Risk of Drinking Water Disinfection Byproducts, 2007.

US Environmental Protection Agency, Scientific and Technological Achievement Award, Update and Perspective on Trichloroethylene Risk, 2007.

US Environmental Protection Agency, Scientific and Technological Achievement Award, Incorporating Metabolic Data in Uncertainty Factors, 2007

US Environmental Protection Agency, Superior Accomplishment Recognition Award (for postdoctoral mentoring), 2007.

US Environmental Protection Agency, Superior Accomplishment Recognition Award (for publication of text on toxicokinetics in risk assessment), 2007.

US Environmental Protection Agency, Office of Research and Development Teamwork Award for Multidisciplinary Approach to Develop and Apply Toxicokinetic Measures in Risk Assessment, 2006.

US Environmental Protection Agency, Bronze Medal for Report on Applications of Physiologically Based Pharmacokinetic Modeling to Risk Assessment, 2006.

US Environmental Protection Agency, Superior Accomplishment Recognition Award (for body of work on PBPK modeling of human variability), 2006.

US Environmental Protection Agency, Superior Accomplishment Recognition Award (for contribution to staffing plan), 2006.

Society of Toxicology, Risk Assessment Specialty Section, 2005 “Top-Ten” Best Paper Award for Risk Assessment Science (Chem Res Toxicol 18:475-485, 2005).

US Environmental Protection Agency, Bronze Medal for Health Risk Assessment Approach for Trichloroethylene, 2005.

US Environmental Protection Agency, Bronze Medal for Methods for Cumulative Risk Assessment, 2005.

US Environmental Protection Agency, Superior Accomplishment Recognition Award (for significant scientific publication), 2005.

Human and Ecological Risk Assessment (journal), Human Risk Assessment paper of the year, 2004 (HERA,10:39-55).

US Environmental Protection Agency, Bronze Medal for Health Risk Assessment for Boron and Compounds, 2004.

U.S. Environmental Protection Agency, Superior Accomplishment Award for Leadership of Toxicology and Risk Assessment conference, 2004.

Society of Toxicology, Risk Assessment Specialty Section, 2003 “Top-Ten” best Paper Awards for Risk Assessment Applications (Risk Anal. 23:1221-1238, 2003).

U.S. Environmental Protection Agency, Team Award for advanced risk methodology research and two reports on cumulative and Mixtures risk assessment, 2003.

Society of Toxicology, Risk Assessment Specialty Section Best Abstract Award (Incorporation of Enzymes Variance into Risk Assessment), 2002.

National Institute for Occupational Safety and Health, Alice Hamilton Award for Scientific Excellence in Occupational Safety and Health, 2001.

U.S. Environmental Protection Agency, Bronze Medal for Comparative Risk Framework Methodology, 2000.

Society of Toxicology, Risk Assessment Specialty Section Best Abstract Award (Human Pharmacokinetic Variance in Risk Assessment), 2000.

Society of Toxicology, Risk Assessment Specialty Section Outstanding Platform Presentation (Translation of Animal Effects to Human Health Conditions), 2000.  
U.S. Environmental Protection Agency, Superior Accomplishment Recognition Award for Applied Pharmacokinetics, 1999.  
U.S. Army, Commendation Medal (Toxicology Methods Development), 1997.  
U.S. Air Force, Science and Technology Achievement Award (Trichloroethylene Metabolism and Pharmacokinetic Modeling), 1996.  
U.S. Air Force, Achievement Medal (Laboratory Organization), 1996.  
U.S. Air Force, Commendation Medal (Scientific Excellence), 1995.

## Memberships

American Industrial Hygiene Association (2016 – present)  
Emergency Response Planning Committee  
International Society for the Study of Xenobiotics (1996 – 2016)  
Society of Toxicology (1990 – present)  
South Central Chapter  
Risk Assessment Specialty Section  
Chemical Mixtures Specialty Section  
Society for Risk Analysis (1994 – present)  
Ohio Chapter  
Dose-Response Specialty Group  
Applied Risk Management Specialty Group  
Security and Defense Specialty Group  
American Legion Post 1, North Little Rock, AR

## List of Publications

Juberg DR, Fox DA, Forcelli PA, Kacew S, Lipscomb JC, Saghir SA, Sherwin CM, Koenig CM, Hays SM, Kirman CR. A perspective on in vitro developmental neurotoxicity test assay results: An expert panel review. *Regul Toxicol Pharmacol* 143:105444, 2023.

Anderson JK, Brecher RW, Cousins IT, DeWitt J, Fiedler H, Kannan K, Kirman CR, Lipscomb J, Priestly B, Schoeny R, Seed J, Verner M, Hays SM. Grouping of PFAS for human health risk assessment: Findings from an independent panel of experts. *Regul Toxicol Pharmacol* 134:105226, 2022.

Pfohl M, Silvestri E, Lipscomb JC, Snyder E, Willison S. Evaluating risk, exposure and detection capabilities for priority chemical threats in water. *J Toxicol Environ Health Part A* 85:622-647, 2022.

Kenyon EK, Eklund C, Pegram RA, Lipscomb JC. Comparison of in vivo derived and scaled in vitro metabolic rate constants for several volatile organic compounds (VOCs). *Toxicol in vitro* 69:105002, 2020.

Lipscomb JC. Purpose driven risk assessment. *Toxicol Pathol* 47:1027-1034, 2019.

Kenyon, EM, Lipscomb, JC, Pegram RA, George BJ, Hines RN. The Impact of Scaling Factor Variability on Risk-Relevant Pharmacokinetic Outcomes in Children: A Case Study Using Bromodichloromethane (BDCM). *Toxicol Sci* 167(2):347-359, 2019.

Juberg DR, Knudsen TB, Sander M, Beck NB, Faustman EM, Mendrick DL, Fowle JR, Hartung T, Tice RR, Lemazurier E, Becker RA, Fitzpatrick SC, Daston GP, Harrill A, Hines RM, Keller DA, Lipscomb JC, Watson D, Bahadori T, Crofton KM. FutureTox III: Bridges for Translation. *Toxicol Sci* 155:22-13, 2017.

Kenyon EM, Eklund C, Lipscomb JC and Pegram RA. 2016. The impact of variation in scaling factors on the estimation of internal dose metrics: a case study using bromodichloromethane (BDCM). *Toxicol Mech Methods* 26:620-626

Meek, ME and Lipscomb JC. 2015. Gaining acceptance for the use of in vitro toxicity assays and QIVIVE in regulatory risk assessment. *Toxicology* 332:112-123.

Bale, AS, Kenyon, E, Flynn, TJ, Lipscomb, JC, Mendrick, DL, Hartung, T and Patton GW. 2014. Correlating *In Vitro* Data to *In Vivo* Findings for Risk Assessment. *ALTEX* 31:79-90.

Chiu, WA, Jinot, J, Scott, CS, Makris, SL, Cooper, GS, Dzubow, RC, Bale, AS, Evans, MV, Guyton, KZ, Keshava, N, Lipscomb, JC, Barone, Jr. S, Fox, JF, Gwinn, MR, Schaum, J and Caldwell, JC. 2013. Assessment Report: Key Findings and Scientific Issues in the Human Health Effects of Trichloroethylene. *Environ Health Perspect*, 121:303-311.

Meek, ME, Barton, HA, Bessems, JG, Lipscomb, JC and Krishnan, K. 2013. Case study illustrating the WHO IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment. *Regul Toxicol Pharmacol* 66:116-129.

Sasso, AF, Schlosser, PM, Kedderis, GL, Genter, M, Snawder, JE, Li, Z, Rieth, S and Lipscomb, JC. 2013. Application of an Updated Physiologically-Based Pharmacokinetic Model for Chloroform to Evaluate CYP2E1-Mediated Renal Toxicity in Rats and Mice. *Toxicol Sci* 131:360-374.

Kaiser, JP, Lipscomb, JC and Wesselkamper, SC. 2012. Putative mechanisms of Environmental Chemical-Induced Steatosis. *Int. J. Toxicol.* 31:551-563.

Colman, J, Rice, GE, Wright, M, Hunter, ES III, Teuschler, LK, Lipscomb, JC, Hertzberg, RC, Simmons, JE, Fransen, M, Osier, M, and Narotsky, MG. 2011. Identification of developmentally toxic drinking water disinfection byproducts and evaluation of data relevant to mode of action. *Toxicol Appl Pharmacol* 254:100-126.

Lambert, JC, Teuschler, LK, Rice, GE, Wright, JM, and Lipscomb, JC. Cumulative Environmental Risk In: Nriagu JO (ed.) *Enc. of Environmental Health*, volume 1, pp. 852-859 Burlington: Elsevier, 2011.

Mazur, CS, Kenneke, JF, Hess-Wilson, JK and Lipscomb, JC. 2010. Differences Between Human and Rat Intestinal and Hepatic Bisphenol-A Glucuronidation and the Influence of Alamethicin on In vitro Kinetic Measurements. *Drug Metab Dispos.* 38:2232-2238.

Barter, ZE, Chowdry, JE, Harlow, JR, Snawder, JE, Lipscomb, JC, Rostami-Hodjegan A. 2008. Co variation of human microsomal protein per gram of liver with age: Absence of influence of operator and sample storage may justify inter laboratory data pooling. *Drug Metab Dispos.* 36:2405-2409.

Hays, SM, Aylward, LL, LaKind, JS, Bartels, MJ, Barton, HA, Boogaard, P, Brunk, C, DiZio, S, Dourson, M, Goldstein, DA, Lipscomb, J, Kilpatrick, ME, Krewski, D, Krishnan, K, Nordberg, M, Okino, M, Tan, Y-M, Viau, C and Yager, JW. 2008. Guidelines for the Derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop. *Regul Toxicol Pharmacol* S1:S4-S15.

LaKind, JS, Aylward, LL, Brunk, C, DiZio, S, Dourson, M, Goldstein, DE, Kilpatrick, ME, Krewski, D, Bartels, M, Barton, H, Boogaard, P, Lipscomb, J, Krishnan, K, Nordberg, M, Okino, M, Tan, C, Viau, C, Yager, JW and Hays, SM. 2008. Guidelines for the Communication of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop. *Regul Toxicol Pharmacol* S16-S26.

Lipscomb, JC and Poet, TS. 2008. In Vitro Measurements of Metabolism for Application in Pharmacokinetic Modeling. *Pharmacology and Therapeutics.* 118:82-103.

Lipscomb, JC, el Demerdash, E and Ahmed, AE. 2008. Haloacetonitriles: Metabolism and Toxicity. *Reviews in Environmental Contamination and Toxicology.* 198:169-200.

Thompson, CM, Sonawane, B, Barton, HA, Dewoskin, RS, Lipscomb, JC, Chiu, WA, and Krishnan, KK. 2008. Approaches for Applications of Physiologically Based Pharmacokinetic Models in Risk Assessment. *J Toxicol Environ Health* 11:1-29.

Barter, ZE, Bayliss, MK, Beaune, PH, Boobis, AR, Carlile, DJ, Edwards, RJ, Houston, JB, Lake, BG, Lipscomb, JC, Pelkonen, OR, Tucker, GT and Rostami-Hodjegan, A. 2007. Scaling factors for the extrapolation of *in vivo* metabolic drug clearance from *in vitro* data: Reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. *Current Drug Metabolism.* 8:33-45.

Chiu, WA, Chen, C, Hogan, K, Lipscomb, JC, Scott, CS and Subramaniam, R. 2007. High-to-low dose extrapolation: issues and approaches. *Human Ecol Risk Assmt.* 13: 46-52.

Chiu, WA, Barton, HA, Dewoskin, RS, Schlosser, P, Thompson, CM, Sonawane, B, Lipscomb, JC and Krishnan, K. 2007. Evaluation of Physiologically Based Pharmacokinetic Models for Use in Risk Assessment. *J App Toxicol.* 27:218-237.

Lambert, JC and Lipscomb, JC 2007. Mode of Action as a Determining Factor in Human Health Risk Assessment of Chemical Mixtures. *Regul Toxicol Pharmacol.* 49:183-194.

- Mahle, DA, Gearhart, JM, Grigsby, C, Mattie, DR, Barton, HA, Lipscomb, JC, and Cook, RS. 2007. Age-Dependent Partition Coefficients for a Mixture of Volatile Organic Solvents in Sprague-Dawley Rats and Humans. *J Toxicol Environ Health* 70:1745-1751.
- Mazur, CS, Kenneke, JF, Tebes-Stevens, C, Okino, MS, Lipscomb, JC. 2007. In Vitro Metabolism of the Fungicide and Environmental Contaminant Trans-Bromuconazole and Implications for Risk Assessment. *J Toxicol Environ Health*. 70: 1241–1250.
- Rodriguez, CE, Mahle, DA, Gearhart, JM, Mattie, DR, Lipscomb, JC, Cook, RS and Barton, HA. 2007. Predicting Age-Dependent Pharmacokinetics of Six Volatile Organic Compounds in the Rat Utilizing Physiologically-Based Pharmacokinetic Modeling. *Toxicol Sci*. 98:43-56.
- Asorey, CM, Muñoz, LM, Pérez-Coll, CS, Lipscomb, JC and Herkovits, J. Efecto Del Ácido Dicloroacético Sobre La Toxicidad Del Cobre Y El Arsénico En Embriones De Anfibio (Effect Of Dicloroacetic Acid On The Toxicity Of Copper And Arsenic In Amphibian Embryos). In: Salud Ambiental y Humana: Una Vision Holistica (Environmental and Human Health: A Holistic Vision). SETAC ISBN - 10: 987-05-1959-8. Ed. Jorge Herkovits pp. 94-96, 2006.
- Chiu, WA, Okino, MS, Lipscomb, JC and Evans, MV. 2006. Issues in the Pharmacokinetics of Trichloroethylene and Its Metabolites. *Env Health Perspec* 114(9):1450-1456.
- Herkovits, J, Muñoz, LM, Asorey, CM and Lipscomb, JC. Amphitox: Un Método Rápido Para Detectar La Toxicidad Remanente Al Proceso De Desinfección Del Agua De Red. (Amphitox: A Fast Method To Detect The Toxicity Of Disinfection Byproducts In Distributed Drinking Water). In: Salud Ambiental y Humana: Una Vision Holistica (Environmental and Human Health: A Holistic Vision). SETAC ISBN - 10: 987-05-1959-8. Ed. Jorge Herkovits pp. 34-36, 2006.
- Beliveau, M, Lipscomb, J, Tardif, R and Krishnan, K. 2005. Quantitative structure-property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. *Chem Res Toxicol*. 18:475-485.
- Gentry, PR, Haber, LT, McDonald, TB, Zhao, Q, Covington, T, Nance, P, Clewell, HJ III, Lipscomb, JC and Barton, HA. 2005. Data for Physiologically-Based Pharmacokinetic Modeling in Neonatal Animals: Physiological Parameters in Mice and Sprague-Dawley Rats. *J Child Health* 2:363-411.
- Teuschler, LK, Rice, GE, Wilkes, CR, Lipscomb, JC and Power, F.W. 2004. A Feasibility Study of Cumulative Risk Assessment Methods for Drinking Water Disinfection By-Product Mixtures. *J Toxicol Environ Health (Part A)*. 67:755-777.
- Lipscomb, JC, Meek, ME, Krishnan, K, Kedderis, GL, Clewell, H and Haber, LT. 2004. Incorporation of Pharmacokinetic and Pharmacodynamic Data into Risk Assessments. *Toxicol Mech Methods*. 14: 145-158.
- Lipscomb, JC, Barton, H, Tornero-Velez, R, Evans, MV, Alcasey, S, Snawder, JE, and Laskey, J.

2004. The Metabolic Rate Constants and Specific Activity of Human and Rat Cytochrome P450 2E1 Toward Chloroform. *J Toxicol Environ Health (Part A)*. 67:537-553.
- Lipscomb, JC. 2004. Evaluating the Relationship between Variance in Enzyme Expression and Toxicant Concentration in Health Risk Assessment *Human Ecol Risk Asses*. 10:39-55.
- Moudgal, CJ, Venkatapathy, R, Choudhury, H, Bruce, RM and Lipscomb, JC. 2003. Application of QSTRs in the Selection of a Surrogate Toxicity Value for a Chemical of Concern. *Env Sci Tech* 37:5228-5235.
- Kedderis, GL and Lipscomb, JC. 2003. Application of *in Vitro* Biotransformation Data and Pharmacokinetic Modeling to Risk Assessment *Toxicol Ind Health* 17:315-321.
- Lipscomb, JC. 2003. How Differences in Enzyme Expression Can Translate into Pharmacokinetic Variance and Susceptibility to Risk. *J. Child. Health* 1:189-202.
- Lipscomb, JC, Teuschler, LK, Swartout, JC, Striley, CAF and Snawder, JE. 2003. Variance of Microsomal Protein and Cytochrome P450 2E1 and 3A Forms in Adult Human Liver. *Toxicol Mech Methods*. 13:45-51.
- Lipscomb, JC, Teuschler, LK, Swartout, J, Popken, D, Cox, T and Kedderis, GL. 2003. The Impact of Cytochrome P450 2E1-dependent Metabolic Variance on a Risk Relevant Pharmacokinetic Outcome in Humans. *Risk Analysis* 23:1221-1238.
- Donohue, JM and Lipscomb, JC. 2002. Health Advisory Values for Drinking Water Contaminants and the Methodology for Determining Acute Exposure Values. *Sci. Tot. Environ*. 288:43-49.
- Fisher, RL, Hasal, SJ, Lipscomb, JC, Gandolfi, AJ and Brendel, K. 2002. Cold and Cryopreservation of Monkey Liver Slices. *Toxicol Mech Methods*. 12:119-133.
- Lipscomb, JC and Kedderis, GL. 2002. Incorporating Human Interindividual Biotransformation Variance in Health Risk Assessment. *Sci. Tot. Environ*. 288:13-21.
- Byczkowski, JZ and Lipscomb, JC. 2001. Physiologically Based Pharmacokinetic Modeling of the Lactational Transfer of Methylmercury. *Risk Anal*.21:869-882.
- Lash, LH, Fisher, JW, Lipscomb, JC and Parker, JC. 2000. Metabolism of Trichloroethylene. *Environ Health Perspec* 108 (Supl 2): 177-200.
- Lipscomb, JC, Byczkowski, JZ and Harvey, T. Physiologically Based Pharmacokinetic Modeling of the Lactational Transfer of Methylmercury. Proceedings of the Sixth International Symposium on Metal Ions in Biology and Medicine, San Juan, Puerto Rico, USA, May 7-10, 2000, (J. Centeno, P. Collery, G. Vernet, et al., eds.), John Libbey Eurotext, Paris, 2000.
- Moudgal, CJ, Lipscomb, JC and Bruce, RM. 2000. Potential Health Effects of Drinking Water Disinfection Byproducts Using Quantitative Structure Toxicity Relationship. *Toxicology* 147:109-

131.

Murphy, P, Rice, G, Teuschler, L, Boutin, B, Brown, M, Clark, R, Cohen, J, Harvey, T, Lipscomb, J, Miltner, R, Papa, L and Rheingans, R. 2000. A Comparative Risk Assessment Methodology to Assess Drinking Water Treatment Technologies. Proceedings of the 6<sup>th</sup> National Drinking Water and Waste Water Treatment Technology Transfer Workshop. Kansas City, MO, August 2-4, 1999. (Online at: [http://www.epa.gov/region07/programs/wwpd/workshop99/region7workshop\\_comparative\\_ra.pdf](http://www.epa.gov/region07/programs/wwpd/workshop99/region7workshop_comparative_ra.pdf)).

Snawder, JE and Lipscomb, JC. 2000. Interindividual Variance of Cytochrome P450 Forms in Human Hepatic Microsomes: Correlation of Individual Forms with Xenobiotic Metabolism and Implications in Risk Assessment. *Regul. Toxicol. Pharmacol.* 32:200-209.

Teuschler, LK, Gennings, C, Stiteler, WM, Hertzberg, RC, Colman, JT, Thiyagarajah, A, Lipscomb, JC, Hartley, WR and Simmons, JE. 2000. A Multiple-Purpose Design Approach to the Evaluation of Risks from Complex Mixtures of Disinfection By Products (DBPs). *Drug Chem Toxicol.* 23(1):307-321.

Teuschler, LK, Rice, G, Lipscomb, JC and Swartout, J. 2000. Extrapolation Issues in Human Health Risk Assessment: Methods for Potential Use in Sex-Specific Health Evaluations. Proceedings of the Annual Meeting of the American Statistical Association. Indianapolis, IN. Aug. 13-17, 2000. American Statistical Association. pp. 50-59.

Courson, DL, Mattie, DR, English, JH, Lipscomb, JC. 1999. Identifying Potential Human Health Risks of Combustion Byproducts from Aerospace Advanced Composite Materials. Proceedings of the Smoke/Obscurants Symposium XX, US Army, Edgewood Arsenal, MD. ERDEC-CR-270 (STCTR3192), pp. 195- 202.

Lash, LH, Lipscomb, JC, Putt, DA and Parker, JC. 1999. Glutathione Conjugation of Trichloroethylene in Human Liver and Kidney: Kinetics and Individual Variation. *Drug Metab Dispos* 27:351-359.

Griffin, JM, Lipscomb, JC and Pumford, NR. 1998. Covalent Binding of Trichloroethylene to Proteins in Human and Rat Hepatocytes. *Tox Lett* 95:173-81.

Lipscomb, JC and Garrett, CM. 1998. Effect of Organ Procurement Conditions on Cytochrome P-450 Activity in Rat Liver Microsomes. *In Vitro Mol Toxicol* 11:265-270.

Lipscomb, JC, Fisher, JW, Confer, PD and Byczkowski, JZ. 1998. In Vitro to in Vivo Extrapolation for Trichloroethylene Metabolism in Humans. *Toxicol Appl Pharmacol* 152:376-387.

Lipscomb, JC, Confer, PD, Miller, MR, Stamm, SC, Snawder, JE and Bandiera, SM. 1998. Metabolism of Trichloroethylene and Chloral Hydrate by the Japanese Medaka *in vitro*. *Environ Toxicol Chem* 17:325-332.

Lipscomb, JC, Garrett, CM and Snawder, J. 1998. Use of Kinetic and Mechanistic Data in Species

Extrapolation of Bioactivation: Cytochrome P-450 Dependent Trichloroethylene Metabolism at Occupationally Relevant Concentrations. *J Occup Health* 40:110-117.

Lipscomb, JC, Buttler, GW and Confer, PD. 1997. Chloral Hydrate Formation in the Japanese Medaka Minnow. *Annals Clin Lab Sci* 27:158-163.

Lipscomb, JC, Garrett, CM, and Snawder, JE. 1997. Cytochrome P450-dependent Metabolism of Trichloroethylene: Interindividual Differences in Humans. *Toxicol Appl Pharmacol*, 142:311-318.

Lipscomb, JC, Kuhlmann, KJ, Cline, JM, Larcom, BJ, Peterson, RD and Courson, DL. 1997. Combustion Products from Advanced Composite Materials. *Drug Chem Toxicol* 20:281-192.

Moghaddam, AP, Abbas, R, Fisher, JW and Lipscomb, JC. 1997. Role of Mouse Intestinal Microflora in Dichloroacetic Acid Formation, an *in vivo* Study. *Human Exptl Toxicology* 16:629-635.

Barton, HA, Flemming, CD and Lipscomb, JC. 1996. Evaluating Human Variability in Chemical Risk Assessment: Hazard Identification and Dose-Response Assessment for Non-cancer Oral Toxicity of Trichloroethylene. *Toxicology*, 110:271-287.

Lipscomb, JC, Mahle, DA, Brashear, WT and Garrett, CM. 1996. A Species Comparison of Chloral Hydrate Metabolism in Blood and Liver. *Biochem Biophys Res Commun* 227(2):340-350.

Moghaddam, AP, Abbas, RR, Fisher, JW, Stavrou, S and Lipscomb, JC. 1996. Formation of Dichloroacetic Acid by Rat and Mouse Gut Microflora, an *in vitro* Study. *Biochem Biophys Res Commun* 228:639-645.

Witzmann, F, Coughtrie, MWH, Fultz, C and Lipscomb, J. 1996. Effect of Structurally Diverse Peroxisomal Proliferators on Rat Hepatic Sulfotransferase. *Chem Biol Interact* 99:73-84.

Witzmann, FA, Fultz, CD and Lipscomb, JC. 1996. Toxicant-induced Alterations in Two-Dimensional Electrophoretic Patterns of Hepatic and Renal Stress Proteins. *Electrophoresis* 17:198-202.

Lipscomb, JC, Mahle, DA, Brashear, WT and Barton, HA. 1995. Dichloroacetic Acid: Metabolism in Cytosol. *Drug Metab Dispos* 23:1202-1205.

Witzmann, F, Fultz, C and Lipscomb, J. 1995. Comparative 2D-Electrophoretic Mapping of Human and Rodent Hepatic Stress Proteins as Potential Biomarkers. *Applied and Theoretical Electrophoresis*, 5:113-117.

Jarabek, AM, Fisher, JW, Rubenstein, R, Lipscomb, JC, Williams, RJ, Vinegar A, and McDougal, JN. 1994. Mechanistic Insights Aid the Search for CFC Substitutes: Risk Assessment of HCFC-123 as an Example. *Risk Analysis* 14(3):231-250.

Scallet, AC, Slikker, W, Jr, Holson, R., Lipe, GW, Lipscomb, JC, Rountree, RL, Stewart, CW and

Matthews, JC, 1992. Age and Dietary Factors in Hippocampal Sensitivity to Trimethyltin. *Ann. N.Y. Acad. Sci.* 648:340-342.

Leakey, JEA, Cunny, HC, Bazare, J, Webb, P, Lipscomb, JC, Slikker, W, Jr. Feuers, RJ, Duffy, PH and Hart, RW, 1989. Effects of Aging and Caloric Restriction on Hepatic Drug Metabolizing Enzymes in the Fischer 344 Rat. II: Effects on Conjugating Enzymes. *Mech. Age. Devel.* 48:157-166.

Lipscomb, JC, Paule, MG, and Slikker, W, Jr., 1989. The Disposition of <sup>14</sup>C-Trimethyltin in the Pregnant Rat and Fetus. *Neurotoxicol. Teratol.* 11:185-191.

Lipscomb, JC, Paule, MG, and Slikker, W, Jr, 1986. Fetomaternal Kinetics of Trimethyltin. *Neurotoxicology* 7(2):581-590.

Slikker, W, Jr, Ali, SF, Lipscomb, JC and Denton, R, 1985. Time-Course Alterations in the Tremor and Muscarinic Receptor Binding Produced by Trimethyltin. *Proc. West. Pharmacol. Soc.* 28:139-142.

### **Book Chapters**

Lipscomb, JC. Quantitative non-default uncertainty factors for risk assessment. *Encyclopedia of Toxicology* (Fourth Edition, P. Wexler, Ed.), Academic Press/Elsevier, Amsterdam, New York (in press, 2023)

Lipscomb JC, Kuhlman CL. 2021. Toxicity data as the basis for acute and short-term emergency exposure guidance. In: *Toxicological Risk Assessment* (A. Tsatsakis, ed), Elsevier.

Lipscomb JC. Application of quantitative dose response data in risk assessment and the incorporation of high throughput data, pp 559-572. In: *Handbook of Developmental Neurotoxicology* (Slikker, Paule, Cheng, eds.) Academic Press, New York, 2018.

Lipscomb, JC, Maples-Reynolds, N, Mumtaz, M. Multiple Chemical Exposures and Risk Assessment. In: *Computational Toxicology* (B. Fowler, Ed). Elsevier, New York, New York, 2013.

Lipscomb, JC, Haddad, S, Poet, T, and Krishnan, K. Physiologically Based Pharmacokinetic (PBPK) Models in Toxicity Testing and Risk Assessment. In: *New Technologies for Toxicity Testing*, (M Balls, RD Combes, N Bhogal, eds.). Landes Bioscience and Springer Science+Business Media, Boston, MA, 2012.

Lipscomb, JC, Lambert, JC and Teuschler, LK. Chemical Mixtures and Cumulative Risk Assessment, 253-281. in: *Principles and Practice of Mixtures Toxicology* (M. Mumtaz., ed.), Wiley, 2010.

Krishnan, K, Loizou, GD, Spendiff, M, Lipscomb, JC and Andersen, ME. PBPK Modeling: A Primer. In: Quantitative Modeling in Toxicology (K. Krishnan and M. Andersen, eds), Wiley, 2010.

Lipscomb, JC. Toxicokinetics for Drinking Water Risk Assessment. pp 91-122, In: Drinking Water Risk Assessment, B. Howd, ed., John Wiley and Sons, Hoboken, New Jersey. 2008.

DeWoskin, RS, Lipscomb, JC and Thompson, C. 2007. Pharmacokinetic and Physiologically Based Pharmacokinetic Models in IRIS assessments. In: Lipscomb JC and Ohanian EV (eds), Toxicokinetics and Risk Assessment. Informa Healthcare Publishers, New York, NY.

Lipscomb, JC, Lambert, JC, and Mumtaz, M. The Toxicity and Risk of Chemical Mixtures. In: Computational Toxicology: Risk Assessment for Pharmaceutical and Environmental Chemicals (S. Ekins, Ed) John Wiley & Sons, New York. 2007.

Robinson, PJ, Gearhart, JM, Mahle, DA, Merrill, EA, Sterner, TR, Lipscomb, JC, and Yu, KO. 2007. Considerations of Design and Data when Developing Physiologically-Based Pharmacokinetic Models In: Lipscomb JC and Ohanian EV (eds), Toxicokinetics and Risk Assessment. Informa Healthcare Publishers, New York, NY.

Rice, G, Teuschler, LK, Moudgal, C, Bruce, B, Murphy, P, Lipscomb, JC, Miltner, RJ, Richardson, S, Clark, RM and Cohen, J. Risk Assessment of Complex Mixtures of Disinfection Byproducts (DBPs): Methods for Considering Unidentified DBPs. In: Microbial Pathogens and Disinfection By-products in Drinking Water: Health Effects and Management of Risks. Eds. GF Craun, FS Hauchman, DE Robinson. ILSI Press. Washington, D.C. pp. 571-580, 2001.

Rice, G, Murphy, PA, Teuschler, LK, Lipscomb, JC, Boutin, BK, Brown, ME, Clark, RM, Rheingans, RD and Cohen, J. U.S. EPA's Comparative Risk Assessment. In: Microbial Pathogens and Disinfection By-products in Drinking Water: Health Effects and Management of Risks. Eds. GF Craun, FS Hauchman, DE Robinson. ILSI Press. Washington, D.C. pp. 371-394, 2001.

Lipscomb, JC and Confer, PD. Human Hepatocytes, A Novel Animal Alternative. In: Toxicity Assessment Alternatives: Methods, Issues, Opportunities (H. Salem and S.A. Katz, eds.), Humana Press, Totowa, NJ, pp. 227-240, 1999.

Channel, S, Dodd, D, Fisher, J, George, M, Lipscomb, J, McDougal, J, Vinegar, A and Williams, J. Supporting Documentation for the Exposure Guidance Levels for Hydrofluorocarbon-123. In: Toxicity Alternatives to Chlorofluorocarbons: HFC-134a and HCFC-123, Committee on Toxicology, National Research Council, National Academy Press, Washington, D.C. (1996).

## **Technical Reports**

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Chemical Warfare Nerve Agents GA, GB, GD, GE, GF, Chlorosoman and Chlorosarin. U.S Environmental

Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. April, 2019. (Restricted distribution).

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Sulfur Mustard. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. April, 2019. (Restricted distribution).

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Acrolein. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. June, 2018. (Restricted distribution).

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Chlorine. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. February, 2018. (Restricted distribution).

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Malathion. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. February, 2018. (Restricted distribution).

U.S. EPA. (Lipscomb JC). Standing Operating Procedure (SOP) for the development of Provisional Advisory levels (PALs) for hazardous chemicals. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. EPA/600/R-18/224. February, 2018.

U.S. EPA (Lipscomb JC). Provisional Advisory Levels for Diborane. U.S Environmental Protection Agency, Office of Research and Development, National Homeland Security Research Center, Cincinnati, Ohio. August, 2017. (Restricted distribution).

U.S. EPA (Lipscomb, JC). 2015. Provisional Peer Reviewed Toxicity values for Carbonyl Sulfide. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio.

U.S. EPA. 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Final. EPA/R-14/002F. <http://www2.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf>

U.S. EPA (Lipscomb, JC). 2013. Provisional Peer Reviewed Toxicity Values for Trinitrophenylmethylnitramine (Tetryl). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio.

U.S. EPA. 2011. Toxicological Review and IRIS Risk Assessment for Trichloroethylene. EPA/635/R-09/011F. <http://epa.gov/iris/supdocs/0199index.html>

WHO/IPCS. 2010. Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. World Health Organization, Geneva, Switzerland. [http://www.who.int/ipcs/methods/harmonization/areas/pbpbk\\_models.pdf](http://www.who.int/ipcs/methods/harmonization/areas/pbpbk_models.pdf)

U.S. EPA (Lipscomb, JC). 2009. Provisional Peer Reviewed Toxicity Values for Commercial Hexane. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio.

U.S. EPA (Lipscomb, JC). 2009. Provisional Peer Reviewed Toxicity Values for n-Hexane. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio.

U.S. EPA. (Teuschler, LK, Hertzberg, R.C., Rice, G.E., Lipscomb, J.C., Wright, J.M. and Lambert, J.C.). 2007. Concepts, Methods, and Data Sources for Health Risk Assessment of Multiple Chemicals, Exposures, and Effects. EPA/600/R-06/013A.

U.S. EPA. (Lipscomb, JC). 2006. Incorporating Toxicokinetic Data in Uncertainty Factors for Non-cancer Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. (NCEA-C-1669; APM462)

U.S. EPA (Chiu, W., Krishnan, K., Barton, H., DeWoskin, R., Foureman, G., Lipscomb, J., Schlosser, P., Sonawane, B, Thompson, C.) 2006. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. EPA/600/R-05/043A.

U.S. EPA. (Lipscomb, JC). 2006. Exposures and Internal Doses of Trihalomethanes in Humans: Multi-Route Contributions from Drinking Water. Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. EPA/R-06/087.

U.S. EPA (Lipscomb, JC). 2005. Provisional Peer Reviewed Toxicity Values for Bis(2-chloroethoxy)methane. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio.

U.S.EPA (Lipscomb, JC). 2005. Application of PBPK Modeling to Examine Tissue Dosimetry in Chronic Disease: Examination of Feasibility. EPA/600/Q-06/001.

U.S. EPA. (Lipscomb, JC and Kedderis, GL). 2005. Use of Physiologically Based Pharmacokinetic Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk: Final Report for Cooperative Agreement. ORD/NCEA. Cincinnati, OH. EPA/600/R-06-014A.

Clewell HJ III, Covington TR, Fisher JW, Chiu W, Lipscomb J, Blancato J, Hack, E, Mattie D, Okino M, Power F, Zhao QJ. 2004. Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Prepared for the U.S. Air Force, prepared by the USAAF-EPA TCE PBPK Workgroup.

Hack, E, Zhao QJ, Clewell HJ III, Fisher JW, Lipscomb J, Blancato J, Covington TR, Mattie DR, Okino M, Power F. 2004. Markov Chain Monte Carlo Analysis Of Harmonized Physiologically-Based Pharmacokinetic Model Of Trichloroethylene And Its Metabolites

Prepared For: United States Air Force. October 14, 2004. Available at:  
<http://www.TERA.org.vera/tce/MCMCreport%20final.pdf>

U.S. EPA (Smallwood, CS, Swartout, JC, Lipscomb, JC). 2004. Toxicological Review and Integrated Risk Information System Summary for Boron and Compounds.

U.S. EPA (Teuschler, L.K., Rice, G.E. and Lipscomb, J.C.) 2003. Developing Relative Potency Factors for Pesticide Mixtures: Biostatistical Analyses of Joint Dose-Response.

U.S. EPA (Teuschler, L.K., Rice, G.E. and Lipscomb, J.C.) 2002. The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Product Mixtures. NCEA-C-1257

U.S. EPA (Lipscomb, J.C. and Cubbison, C.) 2000. Carcinogenicity and Genotoxic Effects of Selected Drinking Water Disinfectants and Disinfection Byproducts. NCEA-C-0843.

U.S. EPA (Lipscomb, J.C. and Pereira, M.A.) 2000. Comparison of Genetic Damage in Tissues of Research Animals Exposed to Drinking Water Disinfectants/Disinfection Byproducts with the Genetic Damage Expressed in Archived Samples of Human Tumor Tissue from DBP Target Organs. NCEA-C-0900.

U.S. EPA (Teuschler, L.K., Lipscomb, J.C., Rice, G.E., Hertzberg, R.C.) 2000. Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. NCEA-C-0791.

U.S. EPA. (Lipscomb, J.C. and Cubbison C.) 1999. Reproductive and Developmental Toxicity Summary for Selected Disinfection Byproducts. NCEA-C-0653.

U.S. EPA (Teuschler, L.K., Lipscomb, J.C., Hertzberg, R.C.) 1999. Research Report on The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) in Drinking Water. NCEA-C-0664.

Lipscomb, J.C. and Garrett, C.M. 1997. Effect of Organ Procurement Conditions on Cytochrome P450 Activity in the Rat. U.S. Air Force Technical Report No. AL/OE-TR-1997-0001.

Courson, D.L., Flemming, C.D., Kuhlmann, K.J., Lane, J.W., Grabau, J.H., Cline, J.M., Miller, C.R., Larcom, B.J., and Lipscomb, J.C. 1996. Smoke production and Thermal Decomposition Products from Advanced Composite Materials. U.S. Air Force Technical Report No. AL/OE-TR-1996-0124.

Lipscomb, J.C., Buttler, G.W. and Confer, P.D. 1996. Trichloroethylene and Chloral Hydrate Metabolism in the Japanese Medaka Minnow (*Oryzias latipes*) *in vitro*. U.S. Air Force Technical Report No. AL/OE-TR-1996-0085.

Silvers, L.A., Garrett, C.M., Walsh, M.J., Mahle, D.A., Buttler, G.W., Southwell, S.A., and Lipscomb, J.C. 1996. The Metabolism and Toxicity of Trichloroethylene in Isolated Hepatocytes of the Rat and Human. U.S. Air Force Technical Report No. AL/OE-TR-1996-0017.

Garrett, C.M., Lipscomb, J.C., Hoover, D.K., and Mahle, D.A. 1995. A Species Comparison of the Metabolism of Chloral Hydrate to Trichloroethanol *in vitro*. U.S. Air Force Technical Report No. AL/OE-TR-1995-0056.

Garrett, C.M., Mahle, D.A., Stavrou, S., and Lipscomb, J.C. 1995. Isolated Perfused Small Intestine - Application for Absorption and Metabolism of Trichloroethylene in the Fischer 344 Rat. U.S. Air Force Technical Report No. AL/OE-TR-1995-0064.

Lipscomb, J.C., Hoover, D.K., Bishop, C.T., Mahle, D.A., Brashear, W.T., Buttler, G.W., and Garrett, C.M. 1995. The *in vitro* Metabolism of Chloral Hydrate. I. Kinetics of Trichloroacetic Acid and Trichloroethanol Formation in Rat and Mouse Liver. U.S. Air Force Technical Report No. AL/OE-TR-1995-0012.

Lipscomb, J.C., Garrett, C.M., Mahle, D.A., and Buttler, G.W. 1995. Dichloroacetic Acid Metabolism *in vitro*. II. Kinetics in Hepatic Cytosol. U.S. Air Force Technical Report No. AL/OE-TR-1995-0055.

Lipscomb, J.C., Garrett, C.M., Mahle, D.A., and Snawder, J.E. 1995. The Effect of Trichloroethylene on Form-Selective Cytochrome P-450 Activities in the Rat, Mouse and Human. U.S. Air Force Technical Report No. AL/OE-TR-1995-0063.

Lipscomb, J.C., Walsh, M.J., Caldwell, D.C. and Narayanan, L. 1995. Inhalation Toxicity of Vapor Phase Lubricants. U.S. Air Force technical Report No. AL/OE-TR-1997-0090.

Mahle, D.A., Buttler, G.W., and Lipscomb, J.C. 1995. Dichloroacetic Acid Metabolism *in vitro*. I. Investigation of the Factors Influencing Dichloroacetic Acid Metabolism. U.S. Air Force Technical Report No. AL/OE-TR-1995-0083.

Barton, H.A., Byczkowski, J.Z., Channel, S.R., Jarnot, B.M., Lipscomb, J.C., and Williams, R.J. 1994. Trichloroethylene: Metabolism and Other Biological Determinants of Mouse Liver Tumors. U.S. Air Force Technical Report No. AL/OE-TR-1994-0135.

Lipscomb, J.C., Leakey, J.E.A., and Slikker, W. Jr. 1990. Effect of Trimethyltin on Rat Hepatic Glutathione Transferase *in vivo* and *in vitro*. U.S. Food and Drug Administration, National Center for Toxicological Research, NCTR Technical Report E-6447.

Lipscomb, J.C., Paule, M.G., and Slikker, W. Jr. 1987. The Transplacental Pharmacokinetics of Trimethyltin. U.S. Food and Drug Administration, National Center for Toxicological Research, NCTR Technical Report E-6385.

Lipscomb, J.C., Paule, M.G., and Slikker, W. Jr. 1986. Pharmacokinetics of 14C-Trimethyltin in the Rat. U.S. Food and Drug Administration, National Center for Toxicological Research, NCTR Technical Report E-6305.

### **Invited Presentations/Committees**

Toxicology Excellence in Risk Assessment (TERA), Cincinnati, OH. Board of Directors 2022 – present

National Academies of Science, Engineering and Medicine, Committee to Review of DOD's Revised Approach to Deriving an Occupational Exposure Level for Trichloroethylene (TCE). 2022 – present.

*Toxicological Sciences*. Editorial Board, 2000 – present; Interim Co-Editor in Chief, January-September, 2013; Associate Editor, 2006 – 2014.

*Toxicology Reports*. Associate Editor 2014 – 2022; Editorial Board 2022 - present.

*Toxicology Mechanisms and Methods*. Associate Editor, 2006 – Present.

*Ad hoc* reviewer for *Inhalation Toxicology*, *Biochemical Pharmacology*, *Environmental Health Perspectives*, *Ecotoxicology and Environmental Safety*, *Neurotoxicology*, *Regulatory Toxicology and Pharmacology*, *Food and Chemical Toxicology*, *International Journal of Toxicology*, and *Toxicology and Applied Pharmacology*.

American Industrial Hygiene Association, Emergency Response Planning Guideline Committee, 2016 - present.

Independent Peer Review Panel for Mode of action Review for Reproductive and Developmental Effects in Mice, Scipinion, LLC, 2024.

External Peer Reviewer for Environmental Protection Agency Advances in Dose Addition for Chemical Mixtures: A White Paper. US EPA (2023), Risk Assessment Forum.

Mammalian Physiology as the Basis For In Vitro to In Vivo and Route to Route Extrapolation of Doses. Toxicology Excellence for Risk Assessment (TERA) Dose Response Boot Camp for ExxonMobil Biomedical Sciences, Annandale, NJ, October 12, 2023

Modeling the Intact Animal: Applications For In Vitro to In Vivo and Route to Route Extrapolations. Toxicology Excellence for Risk Assessment (TERA) Dose Response Boot Camp, Cincinnati, OH, September 28, 2023.

Route to Route Extrapolation for Risk Assessment. Toxicology Excellence for Risk Assessment (TERA) Dose Response Boot Camp, Cincinnati, OH, May, 2023.

Evaluating exposure to trihalomethane disinfection byproducts via drinking water, Toxicology and Risk Assessment Conference, Dayton, OH, April, 2023.

Independent Peer Review Panel for Cumulative/Mixtures Risk Assessment for Developmental Effects, Scipinion, LLC, 2023.

External Peer Review Panel, US EPA's Systematic Evidence Map for Non-cancer Health Effects of Polychlorinated Biphenyl Mixtures, Versar, Inc. 2022.

Independent Peer Review Panel for USEPA's Approaches for PFAS Grouping and Addressing Human Health Risk Assessment Challenges: Problem Formulation and Review Document. Scipinion, LLC, 2021.

Independent Peer Review Panel for US EPA's Interpretation of In Vitro Developmental Neurotoxicity (DNT) Test Assay Results, Scipinion, LLC, 2021.

American College of Toxicology. Special Topics in Toxicology, eLearning Virtual Seminar, Thresholds and Their Derivation. April 22, 2021.

Invited Peer Reviewer for EPA's Mixtures Similarity Tool (MiST) to support the IRIS Non-cancer PCB Assessment. Versar, Inc, 2021.

Peer Review Panelist, Office of Chemical Safety and Pollution Prevention, Office of Pesticide Policy. FIFRA Scientific Advisory Panel Meeting Minutes and Final Report No. 2020-02. Peer Review of the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment September 15-18, 2020. At: [file:///C:/Users/jlipscomb/Downloads/EPA-HQ-OPP-2020-0263-0054\\_content.pdf](file:///C:/Users/jlipscomb/Downloads/EPA-HQ-OPP-2020-0263-0054_content.pdf)

Invited peer reviewer, CDC/Agency for Toxic Substances and Disease Registry, Toxicological Profile for 1,2-Dichloroethane. June, 2020.

Society of Toxicology/US Food and Drug Administration. *In Vitro* to *In Vivo* Extrapolation of Metabolism Data to Support Physiologically Based Modeling for Route-to-Route Extrapolation, in Colloquium, Route to Route Extrapolation in the 21<sup>st</sup> Century. US Food and Drug Administration, College Park, MD, February 19, 2020.

Society of Toxicologic Pathology. Annual Meeting Session Co-Chair, "Toxicity Assessment Paradigms in Regulatory Pathology", Raleigh, NC, June 25, 2019.

Society of Toxicologic Pathology, invited presentation, Purpose-specific toxicity and risk assessments. Raleigh, NC, June 25, 2019.

Toxicology and Risk Assessment Conference. Risk Assessment Approaches for acute and short-duration exposures, West Chester, OH. April 24, 2018.

University of Louisville, Department of Pharmacology and Toxicology. Course Director and lecturer,

Introduction to Human Health Risk Assessment, 1 hour credit graduate level course. Spring, 2015, 2017, 2020.

International Life Sciences Institute/Health and Environmental Sciences Institute Working Group on

Risk 21: Advancing Health Risk Assessment, Dose Response Sub Team. 2010 – 2017.

University of Arkansas for Medical Sciences, Career Day. Toxicology & Risk Assessment:

Who gets to say how much is too much? And ... why would they say such a thing? Little Rock, AR, October 12, 2017.

Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry.

Provisional Advisory Levels for emergency planning and response. Atlanta, GA. September 21, 2017.

Society of Toxicology, *Data-Derived Extrapolation Factors, Modes of Action, and Target Tissues*

in: Workshop session, Increasing the Utility and Acceptance of Chemical Specific Adjustment Factors--International Experience, Baltimore, MD, March 15, 2017.

US Environmental Protection Agency, Region 5 On Scene Coordinator Training, “Hazard,

Exposure and Risk: Provisional Advisory Levels (PALs)”. Angola, IN. March, 2017.

US Environmental Protection Agency Risk Assessment Forum, Co-Chair Technical Panel:

Developing US EPA Guidance for the Replacement of Default Uncertainty Factors in Human Health Risk Assessment, 2004 – 2015.

U.S. EPA, ORD/NCEA Working Group on Physiologically Based Pharmacokinetic Models for

Risk Assessment/ Pharmacokinetics Working Group. 2004 – 2019; co-lead, 2014 - 2015.

University of Kentucky. Lecture on *Human Health Risk Assessment* in General Toxicology 509.

Graduate Center for Toxicology, Lexington, KY. Annually, 2008 – 2020.

Toxicology and Risk Assessment Conference, Course chair and lecturer, Data Derived Extrapolation

Factors, West Chester, OH, April 4, 2016.

Toxicology and Risk Assessment Conference, Plenary talk, Risk Assessment for Threats and

Consequences, West Chester, OH, April 5, 2016.

Toxicology and Risk Assessment Conference, Risk Characterization lecturer, in: Crash Course in Risk

Assessment, West Chester, OH, April 7, 2016.

Society of Toxicology Continuing Education Course *Human Health Risk Assessment, A Case Study Application of Principles* (Chair and lecturer), New Orleans, LA, March 12, 2016.

University of Kansas Medical Center, Department of Pharmacology and Toxicology, Keynote address

In John Doull Risk Assessment Symposium, *Push Button Risk Assessment*, September 11, 2015.

Society of Toxicology, Planning Committee, Contemporary Concepts in Toxicology Symposium: Future Tox III: In Vitro Data and In Silico Models for Predictive Toxicology. 2014 – 2015.

Society of Toxicology, *A Rational Approach to Using in vitro Data to Improve Health Risk Assessment*, in: Symposium, Incorporating in vitro Pharmacokinetic Data and Tools into Toxicity testing and Risk Assessments: State of the Science, San Diego, CA, March 24, 2015.

Society of Toxicology, Postdoctoral Assembly. *What is Risk Assessment?* in: Careers in Risk Assessment webinar. November 19, 2014.

Ninth Dubai International Food Safety Conference. *Approaches and Sources of Uncertainty in Mixtures and Cumulative Risk Assessment*. Dubai, United Arab Emirates, November 10, 2014.

South Central Chapter, Society of Toxicology. Plenary Lecture, *The Result of an Intentional Exposure to a Career in Toxicology and Risk Assessment, With a Heavy Focus on Dose*. University of Mississippi, Oxford, MS, October 24 2014.

U.S. Environmental Protection Agency, National Center for Environmental Assessment. Preparation

of the Promotion Documentation Package, in: NCEA Technical Qualification Board Boot Camp Seminar, October 22, 2014.

Nationwide Children's Hospital/ The Ohio State University. Postdoctoral Career Seminar. *Risk Assessment: What's a Nice Toxicologist Like You Doing in a Place Like This?* October 17, 2014.

European Food Safety Authority. *Uncertainty in Mixtures and Cumulative Risk Assessment*, in: Scientific Colloquium 21: Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals. 11-12 September 2014, Edinburgh, UK. Report available at: <http://www.efsa.europa.eu/en/supporting/doc/784e.pdf>

American College of Toxicology. *Human Health Risk Assessment*, in: Advanced Comprehensive

Toxicology, August 10, 2014, August 10, 2015. University of Cincinnati, Cincinnati, OH,

Society of Toxicology, Councilor (2011-2014).

Toxicology and Risk Assessment Conference 2014. Trihalomethane Mixtures Risk Assessment Case

Study, in: Workshop, Basic Concepts in Chemical Mixtures Toxicology and Risk Assessment. April 10, 2014.

Toxicology and Risk Assessment Conference 2014. Workshop, Replacing Default Values for Uncertainty Factors (Co-chair). April 10, 2014.

Society of Toxicology *Nondefault Uncertainty Factor Values* in: Continuing Education Course, Methodologies in Human Health Risk Assessment, Phoenix, AZ, March 23, 2014.

Society of Toxicology, Risk Assessment Specialty Section: Councilor 2006-2008; Vice President-elect

2010-11; Vice President, 2011-12; President, 2012-13.

St John's University, Key Note Address: *Application of Pharmacokinetic Information in Health Risk Assessment*. (SOT Tox Scholar visit) Tox Expo 2013, College of Pharmacy & Allied Health Professions, St John's University, Queens, New York, NY. May 2, 2013.

Northern California Chapter, Society of Toxicology. *Toxicokinetics and Risk Assessment: Refining the Dose Response Relationship*. South San Francisco, CA, April 23, 2013.

Society of Toxicology *Applying Your Research Skills in a Key Government Agency*. Education-Career

Development Session: Regulatory Science and Risk Assessment: Lessons for Early Career Scientists on What to Expect and How to Pursue this Career Path, San Antonio, TX, March 13, 2013.

Society of Toxicology *Dose Response Assessment*, in: Continuing Education Course, Basic Principles

of Health Risk Assessment, San Antonio, TX, March 10, 2013.

University of Arkansas for Medical Sciences, Career Day. *Applying Your Research Skills in a Key Government Agency*. (SOT Tox Scholar visit) Little Rock, AR, October 18, 2012.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Workshop participant

and contributor to Effects of Chemical Co-exposures at Doses Relevant for Human Safety Assessments – Technical report No. 115. July – December, 2011.

American Board of Toxicology, Board of Directors. 2006-2010, President 2010.

Society of Toxicology, Member Services Strategy Committee. 2006-2007.

Society of Toxicology, Continuing Education Committee. 2007-2010, Chair 2010.

Toxicology and Risk Assessment Conference for 2012. Steering Committee, Poster Chair. April 30 – May 3, 2012, West Chester, OH.

Toxicology and Risk Assessment Conference, Continuing Education Course: Chemical Specific Adjustment Factors (Chair, lecturer), West Chester, OH, May 3, 2012.

Toxicology and Risk Assessment Conference, *In vitro to in vivo Extrapolation for Application in Physiologically Based Pharmacokinetic Models*, in: Symposium on Correlating in vitro data to in vivo Findings for Health Risk Assessment. West Chester, OH, May 2, 2012.

Toxicology and Risk Assessment Conference, *Physiologically Based Pharmacokinetic Modeling – The Preferred Approach to Dosimetric Adjustment*, in: Symposium on Physiologically Based Pharmacokinetic Modeling. West Chester, OH, May 2, 2012.

Toxicology and Risk Assessment Conference, *Addressing Human Variability in a Cumulative Risk Paradigm*. Lipscomb JC. In Symposium on Factors Contributing to Variability: Conundrums in Occupational Risk Assessment. West Chester, OH, May 2, 2012.

Toxicology and Risk Assessment Conference, *Dose Response Assessment*, in: Continuing Education Course on Physiologically Based Pharmacokinetic (PBPK) Models in Risk Assessment (Chair), West Chester, OH, April 30, 2012.

Toxicology and Risk Assessment Conference, *Computational Approaches and Examples* In Continuing Education Course: Crash Course in Human Health Risk Assessment of Environmental Chemicals, West Chester, OH, April 30, 2012.

Society for Risk Analysis Continuing Education Course, Chemical Specific Adjustment Factors (Chair, Lecturer), Charleston, SC, December 4, 2011.

Toxicology and Risk Assessment Conference for 2011. Steering Committee, Poster Chair. West Chester, OH, April 25 – 28, 2011.

Toxicology and Risk Assessment Conference, *Adverse Effects and the U.S. EPA's Traditional Approach to Chemical Risk Assessment*, in symposium on Choosing an Effect as the basis for Acceptable Human Exposure Limits. West Chester, OH, April 27, 2011.

Toxicology and Risk Assessment Conference, *Dose Response Assessment*, in: Continuing Education Course, Crash Course in Human Health Risk Assessment of Environmental Chemicals, West Chester, OH, April 25, 2011.

Toxicology and Risk Assessment Conference, Continuing Education Course, Dosimetric Adjustment

Methods and Application in Dose Response Assessments, (Chair). West Chester, OH, April 25, 2011.

Society of Toxicology, *Toxicokinetics in Risk Assessment*, in: Best Practices for Developing, Characterizing, and Applying Physiologically Based Pharmacokinetic Models in Risk Assessment. Continuing Education Course (Chair). Society of Toxicology, Washington, D.C., March 6, 2011.

Society of Toxicology, Ohio Valley Chapter, Past President.

Society for Risk Analysis, Ohio Chapter, Past President.

Society for Risk Analysis, Dose-Response Specialty Group, Past President.

Institute for Clinical Pharmacology and Toxicology, Charite - the Medical College of Berlin. *The Dose: Toxicokinetics In Human Health Risk Assessment*, Berlin, Germany, July 13, 2011.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Workshop on Combined Exposure to Chemicals. *Conventional Approaches to Risk Assessment of Mixtures*, Berlin, Germany, July 11, 2011.

University of Antwerp, *Using Toxicokinetic Data in Health Risk Assessment: An Example*. Antwerp, Belgium, February 4, 2011.

SETAC Europe 3<sup>rd</sup> Special Science Symposium, Prospective & Retrospective Environmental Risk

Assessment of Mixtures: Moving from Research to Regulation, *Cumulative Risk Assessment: Theory, Practice and Perspective*. Brussels, Belgium, February 2, 2011.

Health Canada. 2.5-day Professional Development Course, Risk Assessment: Review of Fundamentals & Areas of Advancement, (Course co-chair and lecturer). *Dose-Response Evaluation, Route to Route Extrapolation, Chemical-Specific Adjustment Factors and Introduction to Physiologically Based Pharmacokinetic Modeling*. Ottawa, Ontario, Canada, Spring and Fall annually, 2010 – 2013.

Health Canada. Developmental Toxicity – an Overview (Ron Hood & Associates). *Use of Toxicokinetics in Planning Developmental and Reproductive Toxicity Studies and Data Interpretation*, Ottawa, Ontario, Canada, annually, 2008 – 2011.

Association of Government Toxicologists, *Certification in Toxicology*, Washington, D.C., January, 2011.

Health Canada. Workshop on Current State-of-Knowledge in Health Risk Assessment Approaches

for Drinking Water Chemicals. *Route to Route Extrapolation; Decision Analysis; and , Development and Use of PBPK Models to Translate Toxicity Data*, Ottawa, Ontario, Canada, February 1-2, 2010.

World Health Organization, International Program for Chemical Safety, technical panel for developing Guidance on The Characterization and Application of Physiologically Based Pharmacokinetic Models in health Risk Assessment 2006-2010.

Toxicology and Risk Assessment Conference. *Computational Approaches and Examples* in: Continuing Education Course on Physiologically Based Pharmacokinetic (PBPK) Models in Risk Assessment, April 29, 2010, West Chester, OH.

Ohio Valley Society of Toxicology plenary lecture - *Refining Dose-Response Assessments for Risk Assessment*, Mason, OH, November 6, 2009.

*Journal of Toxicology and Environmental Health*, Guest Editor, Part B Critical Reviews, Genetic Polymorphisms in Xenobiotic Metabolizing Systems and Population Distribution (12:5-6), 2009.

International Society for the Study of Xenobiotics, European Meeting. *Regulation of Environmental Contaminants Based on Interspecies Differences in Distribution*. Lisbon, Portugal, May, 2009.

Toxicology and Risk Assessment Conference. *Evaluating Dose Response Relationships*, in: Continuing Education Course, A Crash Course in Risk Assessment, West Chester, OH, April 27, 2009.

Toxicology and Risk Assessment Conference. *Optimal Expression of Dose – Use of Target Tissue Dose in Cumulative Risk Assessments*, in: Continuing Education Course, Cumulative Risk Assessment Concepts and Methods, West Chester, OH, April 30, 2009.

Society of Toxicology, *Application of Quantitative Toxicokinetic Data in Health Risk Assessment*, in: Continuing Education Course, Principles and Applications of Toxicokinetics, Baltimore, MD, March 15, 2009.

University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, *Why Enzyme Differences Might Not Alter Tissue Distributions of Toxicants: A Risk Assessment Application*, Little Rock, AR, December 18, 2008.

Society for Risk Analysis, Continuing Education Course, Chemical Specific Adjustment Factors: Evaluating and Using Data to Quantify Inter- and Intraspecies Extrapolation for Risk Assessment (Chair, Lecturer), Boston, MA, December, 2008.

Toxicology and Risk Assessment Conference. Continuing Education Course, Workshop on Replacing

Default Values for Uncertainty Factors (Chair, Lecturer). West Chester, OH, April 14, 2008.

Toxicology and Risk Assessment Conference. Continuing Education Course, Evaluation of the Human Relevance of Modes of Action in Animals (Chair, Lecturer). West Chester, OH, April 17, 2008.

Society of Toxicology, *Categorical Default Approaches to Uncertainty Factor Development*, in: Continuing Education Course on Use of Data for Development of Uncertainty Factors in Non-Cancer Risk Assessment (Chair). Seattle, WA, March 16, 2008.

International Congress of Toxicology, *Use of Compound-Specific and General Kinetic Data in Human Health Risk Assessment*, in: Continuing Education Course, Development and Interpretation of Toxicokinetic Data for Risk and Safety Assessments (Chair). Montreal, Quebec, Canada, July 15, 2007.

Society of Toxicology, *Application of Mode of Action and Dose-Response Information in a Chemical Mixtures Risk Assessment*, in a Workshop session on Mode of Action, Charlotte, NC, March 25, 2007.

Midwest Chapter SETAC/Chicago Chapter, SRA meeting, Moving Toward Cumulative Risk, *Internal Doses of Trihalomethanes in Humans Resulting from Drinking Water Uses*, Chicago, IL, March 16, 2007.

U.S. Army, Center for Health Promotion and Preventive Medicine, *Non-Default Values for Uncertainty Factors in Non-Cancer Risk Assessment*, Edgewood Arsenal, Aberdeen Proving Ground, MD, February 28, 2007.

University of Cincinnati, Department of Environmental Health Sciences, Seminar, *How Enzymic Variance Can Influence Internal Doses of Toxicants*. February 21, 2007.

Society for Risk Analysis, Continuing Education Course, Replacing Default Values for Uncertainty Factors with Chemical Specific Adjustment Factors: Reducing Uncertainty in Non-cancer Risk Assessment (Chair, Lecturer), Baltimore, MD, December, 2006.

Society for Risk Analysis, Continuing Education Course, Chemical Specific Adjustment Factors (Chair, Lecturer), Orlando, Florida, December, 2005.

Society of Toxicology, National Capital Area Chapter, *Chemical Mixtures Toxicology and Risk Assessment: Guidance and Methods*, in symposium on Toxicology of Chemical Mixtures, Bethesda, Maryland, May 24, 2005.

U.S. Environmental Protection Agency, Risk Assessment Forum, *Exposure as Internal Doses: Combining Genetic/Genomic Data and Pharmacokinetic Approaches*, in Colloquium - Updating the Guidelines for Exposure Assessment, April 13, 2005.

Society of Toxicology, *Relating Response to Dose; and Use of Compound Specific and General Kinetic Data in Human Risk Assessment*, in Continuing Education Course, Development and Interpretation of Toxicokinetic Data for Risk and Safety Assessment, (Chair), New Orleans, Louisiana, March 6, 2005.

Invited contributor, International Programme on Chemical Safety, Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance document for use of data in dose/concentration-response assessment. World Health Organization, Geneva.

University of Cincinnati, Department of Environmental Health Sciences, lecture *Pharmacokinetics in Human Health Risk Assessment* for graduate Risk Assessment course, January, 2003, May, 2004, May, 2006, February, 2007.

American College of Toxicology, *Toxicokinetics - Approaches in Chemical Risk Assessment*, in Continuing Education Course, Toxicokinetics and Physiologically Based Toxicokinetics in Pharmaceutical and Chemical Safety Assessment, Palm Springs, California, November 7, 2004.

U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, *Using in Vitro Derived Metabolic Rate Constants in Addressing Human Toxicokinetic Variability*, Research Triangle Park, NC, June, 2004.

University of Cincinnati, Department of Environmental Health Sciences, lecture *Interspecies and Intraspecies Extrapolation in Health Risk Assessment* for graduate Risk Assessment course, Cincinnati, OH, May, 2004.

U.S. Environmental Protection Agency Risk Assessment Forum, Chair Technical Panel: Should the U.S. EPA Develop Guidance for Replacing Default Uncertainty Factors?, 2003-2004.

U. S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division, *Chloroform: Inhalation Effects and Pharmacokinetic Extrapolation for Uncertainty Factors*, May, 2003.

Society of Toxicology, *The Multiple Roles of Pharmacokinetics*, in Continuing Education Course, Choice and Application of Classical, Population, or Physiologically Based Pharmacokinetics for Chemical Assessment and Pharmaceutical Development (Chair), Salt Lake City, UT, March 9, 2003.

Purdue University, School of Health Sciences, *Implications of Enzyme Variance for Chemical Susceptibility*, West Lafayette, IN, October 15, 2002.

University of Georgia, Department of Environmental Health Sciences, *Cytochrome P-450 Induced*

*Variance of Chemical Risk: Evaluation by Physiologically-Based Pharmacokinetic Modeling*, Athens, GA, September 18, 2002.

Agency for Toxic Substances and Disease Registry, *Variance in Cytochrome P-450 Activity versus Susceptibility to Risk*, Atlanta, GA, September 17, 2002.

University of Maryland and U.S. EPA, *Metabolic Diversity Among Humans: How and Why Age-Dependent Differences in Enzyme Expression Translate into Differences in Risk-Relevant Pharmacokinetic Outcomes*, Workshop on Biological Variability in Children and implications for Risk Assessment, University of Maryland, College Park, MD, March 4, 2002.

Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, Visiting Scientist, study of metabolic variability for health risk assessment, U. Gundert-Remy, host. Berlin, Germany, 1- 19 October, 2001.

Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, *Variability in Metabolizing Enzymes and Risk Assessment*, Berlin, Germany, 18 October, 2001.

Toxicology and Risk Assessment Conference: Issues and Applications in Toxicology and Risk Assessment, Fairborn, OH, *The Impact of Human Interindividual Biotransformation Variance in Health Risk Assessment*, Fairborn, OH, April 25, 2001.

European Federation of Pharmaceutical Sciences, 7<sup>th</sup> EUFEPS Conference on Optimising Drug Development: Strategies to Assess Drug metabolism/Transport Interaction Potential During Drug Development - Towards a Consensus, *Selection of Liver Samples and Contribution of Expressed Enzymes*, Basel, Switzerland, November 13-15, 2000.

World Health Organization, Temporary Advisor, International Program for Chemical Safety's workshop on Uncertainty and Variability in Risk Assessment, *Case Study D, Inclusion of in vitro Data Describing Human Interindividual Variance of Cytochrome P-450 Metabolism in Pharmacokinetic Models for Risk Assessment*, Berlin, Germany, May, 2000.

University of Cincinnati, College of Pharmacy, Department of Therapeutics, Spring Seminar Series. *Human Interindividual Variance of Cytochrome P-450: Impact on the Disposition of Xenobiotics*, Cincinnati, OH, April 5, 2000.

Society for Risk Analysis, *Out of the frying pan and into the fire? Evaluation of the Health Effects of Drinking Water Disinfection Byproducts*, Atlanta, GA, December, 1999.

Mid-West Cytochrome P-450 Symposium, Purdue University, *Interindividual Variability, In Vitro Data and the Human Health Risk Assessment Process*, West Lafayette, IN, September, 1999.

Tulane University, School of Public Health and Tropical Medicine, Department of Environmental Health Sciences, *In Vitro to in Vivo Extrapolation for Trichloroethylene Metabolism in*

*Humans: Implications for Human Health Risk Assessment of Environmentally Encountered Toxicants*, New Orleans, LA, March 19, 1999.

University of Louisville Department of Pharmacology and Toxicology, *In Vitro to in Vivo Extrapolation for Trichloroethylene Metabolism in Humans*, Louisville, KY, January 14, 1999.

Department of Defense Spring Toxicology Conference, *Increasing the Relevance of Human Health Risk Assessments: The use of Bioavailability Data in Regulatory Decisions*, Wright-Patterson AFB, OH, April 15, 1999.

Chemical Industry Institute of Toxicology, *Extrapolation of Trichloroethylene's Cytochrome P-450 Dependent Metabolism from in vitro to in vivo in the Human*, Research Triangle Park, NC, October 22, 1998.

US Department of Agriculture, Agricultural Research Service, *Appropriate Test Species: Metabolic Differences Between Fish and Mammals*, Stuttgart, AR, August, 1997.

Wright State University, Wright-Step College Preparatory Course, *Practical Benefits of the Life Sciences*, Fairborn, OH, Summer, 1997.

Conference on Issues and Applications in Toxicology and Risk Assessment, Conference Planning Committee and Co-Chair of "Gastrointestinal Tract Toxicity Issues" session and speaker in "Combustion Toxicology" session, Wright-Patterson Air Force Base, OH, April, 1997.

City of Dayton, Ohio, Environmental Advisory Board, 1996-1998.

Department of Defense Working Group on Ecological Risk Assessment, *Metabolism as a Determinant of Appropriateness of Test Species*, Denver, CO, July, 1996.

East Central Region (Ohio) Science Fair Judge and Chair of Air Force's Student Scholarship Program, Fairborn, OH, July, 1996.

Wright State University, Department of Biochemistry and Molecular Biology, Graduate Level Course, *In vitro Methods in Toxicology*, Fairborn, OH, Summer, 1996.

U.S. Environmental Protection Agency and International Life Sciences Institute, Risk Science Institute Working Group on Bioavailability, committee member, 1995-1997.

European Conference on Specificity and Variability in Drug Metabolism. Sponsored by European Concerted Action COST B-1, Besancon, France. *Interindividual Differences in Chloral Hydrate Metabolism Among Human Organ Donors*, May 11, 1995.

U.S. Food and Drug Administration, National Center for Toxicological Research, *Human Variance in the Conversion of Chloral Hydrate to Trichloroethanol and Trichloroacetic Acid*, Jefferson, AR, November, 1995.

University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, *Human Variance in the Conversion of Chloral Hydrate to Trichloroethanol and Trichloroacetic Acid*, Little Rock, AR, November, 1995.

Wright State University, Department of Biochemistry and Molecular Biology Biomedical Sciences Seminar Series, *Inter and Intra-species Differences in the Kinetics of Chloral Hydrate Metabolism*, Fairborn, OH, April, 1995.

Human Tissue Users Group Meeting. *Metabolism of Trichloroethylene by Human Isolated Primary Hepatocytes*, Sponsored by the University of Glasgow and the Alabama Research and Development Corporation, Glasgow, Scotland, 9-11 September, 1995.

Gordon Research Conference on Drug Metabolism, *Trichloroethylene Metabolism by Rat, Mouse and Human Hepatic Microsomes*, Plymouth, NH, July, 1994.

Gordon Research Conference on Drug Metabolism, *Dichloroacetic Acid Metabolism in Human Subcellular Preparations*, Plymouth, NH, July, 1993.

### **Archived Abstracts**

Lipscomb JC, Willison S, Parry E, Chattopadhyay S, Silvestri E, and Snyder E. Determining the Health Protective Capability of Analytical Detection Methods for Short Duration Exposures. International Decontamination Conference, May 9, 2018. Durham NC; Society of Toxicology, March 14, 2018, Society for Risk Analysis, December 11, 2017. Arlington, VA.

Kobylewski-Saucier SE, Taylor ML and Lipscomb JC. Methodology for Deriving Provisional Advisory Levels (PALs) for Chlorine. Society for Risk Analysis, December, 11, 2017. Arlington, VA.

Kenyon EM, Lipscomb JC, Pegram RA and Hines RN. The Impact of Scaling factor variability on Risk-Relevant Toxicokinetic outcomes in Children: A Case Study using Bromodichloromethane (BDCM). Society of Toxicology, March, 2017. Baltimore, MD.

Kyakulaga AH and Lipscomb JC. Risk Values and Exposure Guidance for Ethylene Glycol Monopropyl Ether, a High Production Volume Chemical. Society of Toxicology, March, 2017. Baltimore, MD.

Milanez A, McClanahan M, Koller L, and Lipscomb JC. Provisional Advisory Levels (PALs) for Dimethylamine (DMA). Society of Toxicology, March, 2017. Baltimore, MD.

Lipscomb JC. Choosing Effects and Points of Departure for Provisional Advisory Levels (PALs). Society for Risk Analysis, December 14, 2016. San Diego, CA.

Kuppusamy SP and Lipscomb JC. Isomer-Specific Toxicity profiles for Aminophenols. Society of Toxicology, March, 2016. New Orleans, LA.

Lipscomb JC, Lowit AB, Kenyon EM, Moser VC, Foos BP, Galizia A, Broder M, and Schoeny R.

Data Derived Extrapolation factors: Improving the Quantitative basis for health risk Assessment. Society of Toxicology, March, 2015. San Diego, CA.

Zaccaria K, McClure P, Odin M, Lipscomb JC, Zhao J, and Wesselkamper SC. Adequacy of Available Data to Derive a Provisional Inhalation Toxicity Value for Carbonyl Sulfide. Society of Toxicology, March, 2015. San Diego, CA.

Kenyon E, Eklund CR, Lipscomb JC and Pegram RA. Variation in Scaling Factors Used for in vitro to in vivo Extrapolation (IVIVE) and its Impact on Internal Dose in Rats: A Case Study with Bromodichloromethane (BDCM). Society of Toxicology, March, 2014. Phoenix, AZ.

Kenyon, EM, Pegram, RA, Eklund, C, Lipscomb, JC. The Impact of variation in Scaling Factors on the Estimation of Internal Dose Metrics: A Case Study using Bromodichloromethane. Society of Toxicology, March 11, 2013, San Antonio, TX.

Kenyon EM, Pegram RA, Eklund C, Lipscomb JC. Comparison of in vivo Derived and Scaled in vitro Metabolic Rate Constants for Some Volatile Organic Compounds. Society of Toxicology, March 14, 2012. San Francisco, CA.

Diwan SB, Lipscomb JC, Whalan J, Keshava N, and Shoaf S. Evaluation of Neurological, Cardiac, and Endocrine Effects of Carbon Disulfide Exposure. Society of Toxicology, March 8, 2011. Washington, D.C.

Lipscomb JC, Lowit AB, Broder M, Foos B, Galizia A, Kenyon E, Moser VC, Schoeny R. Data-Derived Extrapolation Factors for Inter- and Intraspecies Extrapolation. Society of Toxicology, March, 2010, Salt Lake City, UT.

Lipscomb, JC and Dourson, M. Promoting Understanding, Use and Best Practice for PBPK Modeling in a Mode of Action Context. Society for Risk Analysis, December, 2009.

Lipscomb, JC, Rice, G. and Lambert, JC. Application of Pharmacokinetic Data in Cumulative Risk Assessments. Society for Risk Analysis, December, 2008.

Hess-Wilson, JK, Lipscomb, JC, and Teeguarden, J. Interference of prostate cancer disease management by bisphenol A: The application of disease-specific parameters to a physiologically based pharmacokinetic model to assess the sensitivity of a unique subpopulation. Society for Risk Analysis, December, 2008.

Rice, G, Teuschler, L, Hertzberg, R, Lipscomb, J, Lambert, J, Wright, M and MacDonnell, M. Grouping Chemicals by Toxicity for Cumulative Risk Assessment. Society for Risk Analysis, December, 2008.

Lipscomb, J.C. Application of Mode of Action and Dose-Response Information in a Chemical Mixtures Risk Assessment, Society of Toxicology, March, 2007.

Hsu, G., Schlosser, P., Cooper, G.S., Lipscomb, J.C., McClure, P. Updating the IRIS Health Assessment for Dichloromethane (Methylene Chloride). Society of Toxicology, March, 2007.

Lambert, J.C. and Lipscomb, J.C. Hazard Identification and Preliminary Dose-Response Assessment of Organotin Plastic Stabilizers Found in Drinking Water. Society of Toxicology, March, 2007.

Lumpkin, MH, Diamond, GL, Kedderis, GL, Odin, MA, White, JR, Teuschler, LK, Rice, GE, Reid, JB and Lipscomb, JC. A Physiologically Based Pharmacokinetic Model of Trihalomethanes in the Pregnant Rat: Identification of Key Data Needs. Society of Toxicology, March, 2006.

Lambert, JC and Lipscomb, JC. Evaluating Toxic Mode of Action of Organotin Plastic Stabilizers: Assessing Health Risks of Mixtures. Society of Toxicology, March, 2006.

Lipscomb, JC and Choudhury, HC. Bis(2-chloroethoxy)methane: Data Evaluation for Human Health Risk Assessment. Society of Toxicology, March, 2006.

Okino, M, Evans, MV, Power, F, Chui, WA, Lipscomb, JC, Blancato, JN and Chen, C. Evaluation of Multiple Pharmacokinetic Modeling Structures for Trichloroethylene. Society of Toxicology, March, 2006.

Lipscomb, JC, Lambert, JC. A Chemical Mixtures Approach to Organotin Plastic Stabilizers Used in Drinking Water Distribution Systems. Society for Risk Analysis, December, 2005.

Okino, MS, Chiu, WA, Evans, MV, Power, FW, Lipscomb, JC, Tornero-Velez, R, Dary, CC, Blancato, JN and Chen, C. Suitability of Using *In Vitro* and Computationally Estimated Parameters in Simplified Pharmacokinetic Models. International Society for the Study of Xenobiotics, October, 2005.

Yang, RSH, Dennison, JE and Lipscomb, JC. A Framework/Approach for Incorporating PBPK Modeling into Cumulative Risk Assessment of Chemical Mixtures. Society of Toxicology, March, 2005.

Hogan, K, Foster, S, Gift, J, Jinot, J, Setzer Jr, W, Lipscomb, J. Application of Quantitative Methods for Evaluating Dose-Response Data in Health Risk Assessments Prepared for the Integrated Risk Information System (IRIS). Society for Risk Analysis, December, 2004.

Marcus, A, Hsu, G, Hammerstrom, K, Chiu, W, Lipscomb, J. Application of Physiologically Based Pharmacokinetic Models in Assessments for the US EPA's Integrated Risk Information System (IRIS). Society for Risk Analysis, December, 2004.

Yang, RSH, Dennison, J, Lipscomb, J. A Framework/Approach for Incorporating PBPK Modeling into Cumulative Risk Assessment for Chemical Mixtures. Society for Risk Analysis, December, 2004.

Lipscomb, JC, Du, J, Swartout, JC, Mahle, DA, Snawder, JE, and Kedderis, GL. Impact of Interindividual Differences for Human Health Risk Assessment: Hepatic Bioactivation of Chloroform. Society of Toxicology, Baltimore, MD, March, 2004.

Mahle, DA, Grigsby, CC, Godfrey, RJ, Gearhart, JM, Barton, HA, Lipscomb, JC and Cook, RS. Comparison of Partition Coefficients for a Mixture of Volatile Organic Compounds in Rats and Humans at Different Life Stages. Society of Toxicology, Baltimore, MD, March, 2004.

Lipscomb, JC, Rice, GE, and Teuschler, LK. The Cumulative Risk of Drinking Water. Society of Toxicology, Salt Lake City, UT, March, 2003.

Herkovits, J, Munoz, LM, Asorey, CM and Lipscomb, JC. Application of Amphitox Assay to Determine the Toxicity of Dichloroacetic and Trichloroacetic Acids. Society of Toxicology, Salt Lake City, UT, March, 2003.

Haber, L, Gentry, P, Zhao, Q, McDonald, T, Nance, P, Bartow, H, VanLandingham, C, Foureman, G, Barton, HA, DeWoskin, RS, and Lipscomb, JC. Physiological Parameters in Developing Rats and Mice. Society of Toxicology, Salt Lake City, UT, March, 2003.

Smallwood, CL, Swartout, J and Lipscomb, JC. Using Toxicokinetic Data for Kinetic Components of the Interspecies and Interindividual Uncertainty Factors for the Boron Reference Dose. Society of Toxicology, Salt Lake City, UT, March, 2003.

Lipscomb, J.C., Du, J., Kedderis, G.L. An Improved Approach to Assessing the Inhalation Risk of Chloroform. Society for Risk Analysis, Baltimore, MD, December, 2003.

Haber, L.T., Gentry, P.R., Foureman, G., Zhao, Q, McDonald, T., Nance, P, Bartow, H, Vanlandingham, C, Barton, H.A., Dewoskin, R, and Lipscomb, J.C. Physiological Parameters for Neonatal Rats and Mice. Society for Risk Analysis, Baltimore, MD, December, 2003.

Rice, GE., Teuschler, L K., Wilkes, C R., Lipscomb, J C., Power, F W. A Cumulative Risk Assessment Method to Evaluate Multiple-Route Exposures to Chemical Mixtures in Drinking Water. Society for Risk Analysis, Baltimore, MD, December, 2003.

Wilkes, C. R., Teuschler, L. K., Rice, G. E., Lipscomb, J.C., Power, F.W. Estimating Multi-Chemical, Multi-Route Cumulative Exposure to Disinfection By- Products (DBPs) in Drinking Water. Society for Risk Analysis, Baltimore, MD, December, 2003.

Tornero-Velez, R, Laskey, J, Barton, H, Lipscomb, JC and Evans, MV. In Vitro Determination of Metabolic Constants for Chloroform in Human Microsomes. Society of Toxicology, Nashville, TN, March, 2002.

Lipscomb, JC, Teuschler, LK, and Swartout, J. Incorporation of Human Interindividual Enzyme

Expression and Biotransformation Variance into Human Health Risk Assessments. Society of Toxicology, Nashville, TN, March, 2002.

Donohue, JM and Lipscomb, JC. Health Advisory Values for Drinking Water Contaminants and the Methodology for Determining Acute Exposure Values, Society for Risk Analysis, New Orleans, LA, December, 2002.

Lipscomb, JC. A Data-informed Framework for the Development of Uncertainty Factors, Society for Risk Analysis, New Orleans, LA, December, 2002.

Swartout J.C., Smallwood C.L., and J.C. Lipscomb Interspecies and Interindividual Toxicokinetic Variability Factors for the Boron Reference Dose. Society for Risk Analysis, New Orleans, LA, December, 2002.

Linsky, C.F., Harrison, R.A., Zhao, G., Barton, H.A., Lipscomb, J.C. and Evans, M.V. 2001. Estimating Chloroform Biotransformation in F344 Liver Using in vitro Techniques and Pharmacokinetic Modeling. *Toxicol Sci* 60(1):291.

Lipscomb, J.C., Teuschler, L.K. and Snawder, J.E. 2001. Human Interindividual variance of Cytochrome P450 and Microsomal Protein in Liver. *Toxicol Sci* 60(1):252.

Pereira, M.A. and Lipscomb, J.C. 2001. Chemical Specific Cancer Relevant Cellular Alterations as Biomarkers for Disinfectant Byproduct Exposure. *Toxicol Sci* 60(1):142.

Thiyagarajah, A., Gennings, C., Getsfrid, W., Lipscomb, J.C., Teuschler, L.K., Cofield, S., Meadows, S., Conerly, O., and Hartley, W.R. 2001. Developmental Toxicity of Bromodichloromethane in the Japanese Medaka (*Oryzias latipes*). *Toxicol Sci* 60(1):334.

Byczkowski, J.Z., Choudhury, H.C. and Lipscomb, J.C. 2000. Physiologically Based Estimates for the Heterogeneity in Cancer Risk Values for Tetrachloroethylene. *Toxicol Sci* 54(1):420.

Hartley, W.R., Lipscomb, J.C., Teuschler, L.K., Gennings, C. and Thiyagarajah, A. 2000. Chronic Toxicity of Chloroform in the Japanese Medaka (*Oryzias latipes*). *Toxicol Sci* 54(1):185.

Lipscomb, J.C., Striley, C.A.F. and Snawder, J.E. 2000. Human Interindividual Variability in the Expression of Cytochrome P450 Forms Critical to Xenobiotic Metabolism. *Toxicol Sci* 54(1):181.

Murphy, P., Rheingans, Cohen, J., Teuschler, L., Lipscomb, J., Clark, R., Miltner, R., Boutin, B., Brown, M., and Harvey, T. 2000. Identifying, Valuing and Comparing Risks and Benefits of Public Drinking Water Treatment Practices: Novel Application of the Quality Adjusted Life Year (QALY) Metric in an Environmental Health Setting. *Epidemiology* 11(4):S108.

Rice, G.E., Lipscomb, J.C., Boutin, B., Brown, M., Clark, R., Cohen, J., Harvey, T., Miltner, D., Murphy, P., Teuschler, L.K., Rheingans, R. and Papa, L.R. 2000. Translating the Results of Risk Characterization into Human Health Conditions (HHC) in USEPA's Comparative Risk Framework Methodology (CRFM). *Toxicol Sci* 54(1):250.

- Thiyagarajah, A., Teuschler, L.K., Lipscomb, J.C., Gennings, C. and Hartley, W.R. 2000. Chronic Pathological Effects from Exposure of Japanese Medaka (*Oryzias latipes*) Embryos to Bromoform. *Toxicol Sci* 54(1):185.
- Byczkowski, J.Z. and Lipscomb, J.C. 1999. The Impact of Experimental Uncertainty and Interindividual Variability on In Vitro to In Vivo Extrapolation for Trichloroethylene Metabolism in Humans. *Toxicol Sci* 48(1S):280.
- Courson, D.L., Kimmel, E.C., Lipscomb, J.C. and Carpenter, R.L. 1999. The Generation of Respirable Particulate and Fibers from the Partial Pyrolyzation of Advanced Composite Materials. *Toxicol Sci* 48(1S):117.
- Teuschler, L.K., Simmons, J.E., Hartley, W.R., Thiyagarajah, A., Lipscomb, J.C. 1999. Categorical Regression Analysis of Bromodichloromethane (BDCM) Liver Toxicity and pathology Data. *Toxicol Sci* 48(1S):86.
- Rice, G., Teuschler, L.K. and Lipscomb, J.C. 1999. Comparative Risks of Drinking Water Treatment Systems. *Toxicol Sci* 48(1S):86.
- Lash, L.H., Putt, D.A., Parker, J.C. and Lipscomb, J.C. 1999. Kinetics and Individual Variation in GSH Conjugation of Trichloroethylene (TRI) in Human Liver and Kidney. *Toxicol Sci* 48(1S):228.
- Lipscomb, J.C., Fisher, J.W., Confer, P.D., and Byczkowski, J.Z. 1999. In Vitro to In Vivo Extrapolation for Trichloroethylene Metabolism in Humans. *Toxicol Sci* 48(1S):141.
- Lipscomb, J.C., Striley, C.A.F. and Snawder, J.E. 1999. Distribution of Three Cytochrome P450 Forms and Activities in Human Hepatic Microsomes from Organ Donors. *ISSX Proceedings* 15:111.
- Moudgal, C.J., Bruce, R.M. and Lipscomb, J.C. 1999. Potential Health Effects of DBPs Using Quantitative Structure Toxicity Relationships. *Toxicol Sci* 48(1S):118-119.
- Kuhlmann, K.J., Narayanan, L., Lipscomb, J.C., Courson, D.L., Langford, R.E. and Dodd, D.E. 1998. Combustion Products of Bismaleimide Resin/Carbon Fiber Composites. *Toxicol Sci* 42(1S):253.
- Courson, D.L., Kuhlmann, K.J., Langford, R.E., Lipscomb, J.C., Mattie, D.R. and Dodd, D.E. 1998. Development of a Novel System to Generate and Characterize Advanced Composite Material Combustion Products During an Animal Exposure. *Toxicol Sci* 42(1S):293.
- Courson, D.L., Lipscomb, J.C. Larcom, B.L. and Cline, J.M. 1997. Thermal Decomposition Products of Advanced Composite Materials. *Fundam Appl Toxicol* 36 (No.1, Part 2): 366.
- Griffin, J.M., Lipscomb, J.C., and Pumford, N.R. 1997. Trichloroethylene-Protein Adducts in Cultured human and Rat Hepatocytes. *Fundam Appl Toxicol* 36 (No.1, Part 2): 320.

- Lipscomb, J.C., Black, R.K., Janicki, T.J., Mahle, D.A., Fisher, J.W. and Abbas, R. 1997. Destruction of Cytochromes P450 *in vivo* by Trichloroethylene: Loss of CYP3A and CYP1A Activities. *Fundam Appl Toxicol* 36 (No.1, Part 2): 317.
- Miller, M.R., Buttler, G.W., Confer, P.D., Bandiera, S.M., Stamm, C., and Lipscomb, J.C. 1997. Trichloroethylene Metabolism by the Japanese Medaka *in vitro*. *Fundam Appl Toxicol* 36 (No.1, Part 2): 350.
- Moghaddam, A.P., Abbas, R., Fisher, J.W. Stavrou, S., and Lipscomb, J.C. 1997. Metabolism of trichloroethylene and Trichloroacetic Acid by Mouse Gut Microflora. *Fundam Appl Toxicol* 36 (No.1, Part 2): 317.
- Snawder, J.E. and Lipscomb, J.C. 1997. Intra-Individual Variation of Cytochrome P450 Forms in Human Hepatic Microsomes: Correlation of Individual Forms with Xenobiotic Metabolism. *Fundam Appl Toxicol* 36 (No.1, Part 2): 25.
- Witzmann, F.A., Fultz, C.J., and Lipscomb, J.C. 1997. Trichloroethylene-Induced Hepatic Protein Pattern Alterations in Mice. *Fundam Appl Toxicol* 36 (No.1, Part 2): 318.
- Garrett, C.M., Mahle, D.A., and Lipscomb, J.C. 1996. Comparison of the *in vitro* Metabolism of Trichloroethylene in Three Species: Rat, Mouse and Human. *Fundam Appl Toxicol* 30 (No.1, Part 2): 318.
- Lipscomb, J.C., Silvers, L., Mahle, D.A., Garrett, C.M., and Confer, P.D. 1996. Trichloroethylene Metabolism by Human Hepatocytes in Primary Culture. *Fundam Appl Toxicol* 30 (No.1, Part 2): 318.
- Huffman, C.M., Hoover, D.K., Mahle, D.A., and Lipscomb, J.C. 1995. A Species Comparison of the Metabolism of Chloral Hydrate to Trichloroethanol *in vitro*. *Toxicologist* 15(1):293.
- Lipscomb, J.C., Huffman, C.M., Buttler, G.W., and Mahle, D.A. 1995. Kinetics and Inhibition of Dichloroacetic Acid Metabolism *in vitro*. *Toxicologist* 15(1):61.
- Lipscomb, J.C., Mahle, D.A., and Garrett, C.M. 1995. Chloral Hydrate Metabolism in Three Mammalian Species. *ISSX Proceedings* 8:294.
- Mahle, D.A., Buttler, G.W., and Lipscomb, J.C. 1995. Investigation of the Factors Influencing Dichloroacetic Acid Metabolism *in vitro*. *Toxicologist* 15(1):195.
- Snawder, J.E., Huffman, C.M., and Lipscomb, J.C. 1995. The Effect of Trichloroethylene on Cytochrome P-450 Form-Specific Activities of Mouse, Rat and Human Microsomes. *Toxicologist* 15(1):118.
- Lipscomb, J.C., Brashear, W.T., Buttler, G.W., Barton, H.A., and Mahle, D.A., 1994. *In Vitro* Metabolism of Dichloroacetic Acid, a Trichloroethylene Metabolite. *ISSX Proceedings* 6:129.

- Lipscomb, J.C., and Garrity, B.L. 1994. The Effect of 1,1,1-Trifluoro-2,2-dichloroethane on Cytochrome P-450 IIE-1-dependent Metabolism. *Toxicologist* 14(1):279.
- Mahle, D.A., Brashear, W.T., and Lipscomb, J.C. 1994. Interspecies Comparison of Trichloroethylene Metabolism *in vitro*. *Toxicologist* 14(1):282.
- Lipscomb, J.C. and Schmidt, W.J. III. 1993. Implications of Differences in Tissue Partitioning Parameters Between HCFC-123 and Halothane. *Toxicologist* 13(1):178.
- Schmidt, W.J., Lipscomb, J.C., Fisher, R.L., Hasal, H.J., Sannuik, J.T., and Brendel, K., 1993. Cryopreservation of Primate Liver Slices. *Toxicologist* 13(1):148.
- Lipscomb, J.C., and Leakey, J.E.A., 1992. The Inhibition of Rat Hepatic Glutathione S-transferase by Trimethyltin *in vitro* and *in vivo*. *Toxicologist* 12(1):416.
- Lipscomb, J.C., and Leakey, J.E.A., 1992. Effect of Trimethyltin on Glutathione and Glutathione S-transferase within the Rat Brain. *FASEB J.* 6(4):A1304.
- Leakey, J.E.A., Wolff, G.L., Bazare, J.J., Jr., and Lipscomb, J.C., 1991. Differential Expression of Hepatic Detoxicating Enzymes in Heavy and Light (C3H x VY) F1 Hybrid Mice Correlates with Increased Susceptibility to Hepatocarcinogenesis. *Toxicologist* 11(1):190.
- Scallet, A.C., Slikker, Jr, W., Ali, S.F., Holson, R., Lipe, G.W., Rountree, R.L., Stewart, C.W. and Lipscomb, J.C., 1991. Aging Sensitizes Hippocampus to Trimethyltin (TMT): Neurohistological, Neurobehavioral and Neurochemical Markers. *Toxicologist* 11(1):168.
- Lipscomb, J.C., Bazare, J.J. Jr., Harmon, J.R., and Leakey, J.E.A., 1990. Comparative Development of the Hepatic Glutathione S-transferase isozymes. *ISSX Proceedings*
- Lipscomb, J.C., Bazare, J.J., Jr., Harmon, J.R., Slikker, W., Jr., Bailey, J.R., and Leakey, J.E.A., 1990. Development of the Hepatic Glutathione S-transferase Isozymes in the Rhesus Monkey (*Macaca mulatta*). *Pharmacologist* 32(3):175.
- Lipscomb, J.C., Leakey, J.E.A., Bazare, J.J., Jr., and Slikker, W., Jr., 1990. Trimethyltin Inhibition of Glutathione S-transferase 3-3 *in vivo*. *Toxicologist* 10(1):298.
- Lipscomb, J.C., Leakey, J.E.A., Bazare, J.J., Jr., Webb, P.J., and Slikker, W., Jr., 1987. The Effect of Trimethyltin on Rat Hepatic Glutathione S-transferase *in vitro*. *Toxicologist* 7(1):169.
- Lipscomb, J.C., Paule, M.G., and Slikker, W., Jr., 1986. The Fetomaternal Disposition of <sup>14</sup>C-Trimethyltin in the Gestational Day 12 Rat. *Teratology* 33(3):66C.
- Paule, M.G., Lipscomb, J.C., and Slikker, W., Jr., 1985. The Kinetics of <sup>14</sup>C-Trimethyltin in the Rat. *Toxicologist* 5(1):173.