Exhibit 90

CAMP LEJEUNE: KIDNEY CANCER

EXPERT REPORT OF

BENJAMIN HATTEN, M.D., M.P.H.

Date: December 8, 2024

Benjamin Hatten MD MPH

II Personal Background/qualifications

By way of introduction, I am a medical toxicologist, emergency physician, and epidemiologist. I am currently an Associate Professor at the University of Colorado School of Medicine with a primary appointment in the Section of Medical Toxicology, Department of Emergency Medicine. In addition, I am an attending physician at the Rocky Mountain Poison and Drug Center as well as a member of Toxicology Associates, Prof. LLC, - a hospital based, single specialty medical group dedicated solely to medical toxicology. I am board certified in both emergency medicine and medical toxicology, and I actively practice both emergency medicine and medical toxicology. Medical toxicology is an American Board of Medical Specialties recognized sub-specialty that deals specifically with human disease associated with any potentially toxic exposure. As a medical toxicologist, I specialize in the assessment, diagnosis, and treatment of adverse effects of pharmaceuticals, other chemicals, natural toxins, envenomations, and any other potential toxicants or toxicological conditions.

I received my M.D. at the University of Texas - Southwestern Medical Center in Dallas, TX. After completion of this degree, I entered residency in emergency medicine at Denver Health Medical Center in Denver, Colorado. Following this, I worked as faculty in the emergency medicine residency program at Denver Health Medical Center and the University of Colorado School of Medicine for a single year. Subsequently, I entered medical toxicology fellowship training at Oregon Health and Science University in Portland, Oregon. During my fellowship, I simultaneously obtained a Masters in Public Health in epidemiology and biostatistics. Upon completion of my Fellowship and M.P.H. degree, I returned to Denver in 2013 and joined the faculty at the University of Colorado School of Medicine, the Rocky Mountain Poison and Drug Center, and Toxicology Associates.

In my role at the University of Colorado School of Medicine and the Rocky Mountain Poison and Drug Center, I provide case-based teaching, didactic instruction, and supervision of clinical care provided by medical and pharmacy students, residents, and medical toxicology fellows-in-training. In addition, I am involved in ongoing research through the University of Colorado School of Medicine and the Rocky Mountain Poison and Drug Center. Furthermore, I have an active practice primarily caring for patients through Toxicology Associates. In all these capacities, I routinely evaluate and treat patients who present with both acute and chronic toxicologic issues, including exposure to toxic substances such as TCE, PCE, Vinyl Chloride and Benzene. I have evaluated and treated thousands of patients with toxicologic conditions during my career. My opinions are based, in part, on my education, training and experience as detailed above and throughout this report. I am being compensated at my usual rate of $750 per hour in connection with this proceeding. A copy of my Curriculum Vitae including a list of my publications is attached.

III Methodology

The approach to determining causation within epidemiology and toxicology involves identification of an exposure and outcome of interest, conducting a comprehensive literature search of human experimental and epidemiologic studies, assessing contributory animal and mechanistic data when available, and systematically reviewing this body of literature. The Bradford-Hill considerations are employed as a framework for organizing discussion when assessing for sufficient evidence of causation. In the case of Camp Lejeune exposures, the standard for causation has been statutorily defined as either “sufficient to conclude that a causal relationship exists” or “sufficient to conclude that a causal relationship is at least as likely as not”. Such a change represents a different and reduced causation

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

standard than typically assessed. In the following paragraphs, a detailed discussion lays out the standard methodology utilized for determination of sufficient causation followed by consideration of the at least "as likely as not" standard.

IV Causation

Prior to discussing individual studies analyzing the potential association between Camp Lejeune water exposure and cancer, it is first important to explain how a medical toxicologist and epidemiologist determines general causation, i.e., is a particular exposure a cause of a specific outcome in humans. Since the 1960s, in particular following Sir Bradford Hill's 1965 address, the scientific community has recognized the need for a structured discussion to determine whether an observed or proposed association of interest is causal. Of note, while epidemiologists use the term "association" to report quantifiable findings when analyzing a dataset derived from a specific population, this term does not imply either a general association in the population at large or provide direct evidence of causation. A stepwise approach offers the most robust and clear means of performing a causation determination, detailed in the following paragraphs.

To begin, an explicit exposure-outcome relationship must be defined prior to any analysis. The discussion requires a distinct exposure and clearly determined outcome. In the context of medical toxicology and epidemiology, the exposure definition needs to involve distinguishing factors beyond simply the name of the substance of interest, ideally including but not limited to timing, chronicity and route of exposure, dosing range, and chemical formulation in order to analyze proposed causal associations. Likewise, defining the outcome of interest requires sufficient detail with respect to organ, tissue, or metabolic processes affected as well as whether the proposed causal pathway is limited to subpopulation(s) or occurs in all humans. Of note, the available body of literature may not contain sufficient data on all aspects of the exposure, requiring interpretation of indirect evidence.

Once the proposed exposure-outcome relationship is sufficiently defined, a robust search of the human literature is performed. Following this, evidence surrounding the proposed exposure-outcome relationship is analyzed systematically. The highest level of potential evidence for causation comes from human studies, either randomized control trials or epidemiological studies, examining the exposure and outcome of interest. These studies must be evaluated with respect to individual study design along with assessing the totality of the body of literature relating to the specific exposure and outcome. Under the "as likely as not" standard, evidence obtained from animal and in vitro studies are sufficient to meet such a standard. In addition, they help elucidate biological plausibility. As a scientific principle, a lack of causality is assumed for any observed association, with the requirement to assemble evidence that rises to the standard of causation in order to reject such an assumption. Under the at least "as likely as not"

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

standard, this means that only the assumption of "less likely than not" need be rejected to establish a causal link.

The evaluation of whether a causal relationship exists employs the elements of the Bradford Hill considerations. As expressed in his original address, Hill correctly cautioned against the use of these factors as a checklist or point system rather than as factors to consider (Hill 1965). Rather, it serves as a framework for summarizing and discussing the evidence. Not every consideration needs to, nor is expected be met in order to reach a causal conclusion. The Hill considerations have been generally accepted by and applied to the field of toxicology (Adami 2011; Guzelian 2005). This begins with assessment of quantitative measures of association, starting with quantifiable measures such as relative risk, in the context of a critical appraisal of the strength of the observed association and consistency of such measures within subpopulations in each study as well as between populations analyzed in various studies. The assessment of strength of association necessarily involves examining the robustness of the methods employed in the underlying studies. The same is true for an assessment of consistency.

Additional points of discussion, as suggested by Sir Austin Bradford Hill, include temporality, dose-response gradient, biological plausibility, coherence, specificity, experiment, and analogy. For a causation analysis within toxicology, strength of association, consistency, dose-response, and experiment (when available) are likely the most robust remaining factors. In particular, demonstration of a dose-response is not essential but provides substantial evidence of causation in the setting of a possible toxic exposure. In addition, such a relationship may be particularly helpful when attempting to extrapolate studied levels of exposure. Of note, temporality, while not the strongest factor in building a case for causation, cannot be ignored in order to find causation as the exposure must occur before the outcome. Finally, biological plausibility is dependent upon the scope of the body of scientific knowledge. Thus, the absence of well-developed mechanistic and animal models does not imply lack of causation.

<u>As likely As Not</u>

Of particular import in the Camp Lejeune proceedings, the standard for causation includes both evidence that is:

a. Sufficient to conclude that a causal relationship exists; or
b. Sufficient to conclude that a causal relationship is at least as likely as not

The robust discussion in the preceding paragraphs provides an overview of the accepted framework for determining whether or not a causal relationship exists. There is a well-developed scientific discourse surrounding this standard as described. A variety of approaches to operationalize the "as likely as not standard" have been proposed.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

For example, The Institute of Medicine suggested a framework in 2008 in the context of Veterans Affairs service-connected conditions (IOM 2008), with "Equipoise and Above" equivalent to "As Likely As Not":

1. Sufficient: The evidence is sufficient to conclude that a causal relationship exists.

2. Equipoise and Above: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.

3. Below Equipoise: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.

4. Against: The evidence suggests the lack of a causal relationship.

As a second example, The Agency for Toxic Substances and Disease Registry (ATSDR) is a governmental organization that published a report examining the evidence surrounding Camp Lejeune exposures and various outcomes of interest, operationalizing the causation discussion per this rubric (ATSDR 2017). The ATSDR application of this framework is rather conservative and more stringent than expressed in the IOM report where "the benefit of the doubt would be given to the veteran" (IOM 2008). Additionally, it is clear that the "equipoise and above" standard does not require a preponderance of evidence but is more accepting of measures of association that cluster around the null. Furthermore, attempts by the ATSDR to satisfy the "as likely as not" standard using quantifiable measures of association are necessarily excessively conservative, given that this is a qualitative evaluation of the body of evidence. Nevertheless, even such a conservative approach safely exceeds the at least "as likely as not" standard, meaning that an exposure-outcome relationship identified as causal using the ATSDR framework is above equipoise.

For ease of discussion, the causation evaluation below utilizes the framework as promulgated by the ATSDR. From a scientific perspective, such a framework is more stringent than the plain language of the statute that established this causation standard. Additionally, there is no universal consensus on how an at least "as likely as not" standard is to be evaluated. The framework from the ATSDR is scientifically valid, methodologically sound and is consistent with my extensive education, training and experience as described above. This discussion is moot in the discussion of kidney cancer as it is clear that the body of evidence supports a determination of sufficient evidence for causation following exposures to the contaminated water at Camp Lejeune. The causal relationship between kidney cancer and the toxins in the water at Camp Lejeune would meet a more stringent "more likely than not" standard. However, in the case of other outcomes, the ATSDR framework provides one of several appropriate means of evaluating causation and was the classification system itself created and chose to use to analyze these same issues.

The standard outlined by the ATSDR (2017) for at least "as likely as not" is as follows:

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is *at least as likely as not*, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

1. The degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality, or

2. A meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, i.e., ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

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

Of note, the ATSDR states that "we did not use confidence intervals to determine whether a finding was "statistically significant", nor did we use significance testing to assess the evidence for causality." Furthermore, "an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10."

<u>Exposures of interest</u>

Exposures of interest in this analysis consist of any individual who lived, worked, or was otherwise exposed for at least 30 days to water at Camp Lejeune beginning August 1, 1953, and ending December 31, 1987. The water systems at Camp Lejeune were contaminated with a mixture of chemicals during this period, including but not necessarily limited to trichloroethylene (TCE), perchloroethylene/tetrachloroethylene (PCE), benzene, and vinyl chloride.

The body of literature that is most directly informative includes human studies of Camp Lejeune exposed individuals as these studies examine the actual, real-world exposure of interest in this analysis. Persons exposed at Camp Lejeune often both lived and worked on the base meaning that daily interactions with compounds of interest were not limited to the jobsite. Furthermore, the use of water from the water system for all aspects of life meant that exposures may not have exclusively consisted of an oral route of intake. Rather, dermal, inhalational, and in utero exposures were also encountered. Of note, inhalational exposures such as showering with contaminated water are likely to represent a much greater intensity of exposure than exclusively oral exposures (Bove 2014a; McKone 1991). This means that exposures at the same estimated level of water contamination are more intense than equivalent occupational exposures where the exposures are limited to certain routes and for limited hours per day.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

The ATSDR utilized a reasonable, but conservative approach in their analysis of route of exposure (ATSDR PHA 2017).

Additionally, the unique mixture of compounds any individual encountered likely varied over time. Epidemiologic studies of exposed individuals from Camp Lejeune provides direct examination of outcomes following the exposure of interest in whatever mixture of compounds occurred at the time of exposure, although exposures were estimated per individual compound. However, it is unlikely that any person on base was exposed to a single compound in isolation, or even a single water system while on base (Rosenfeld 2024). Furthermore, as discussed in this report, the human data from analysis of Camp Lejeune exposures suggests at least an additive, if not synergistic, effect causing an increased risk of kidney cancer from combined exposures (ATSDR PHA 2017, ATSDR 2018; Bove 2014a; Bove 2024a; Bove 2024b). This means that the combination of chemicals causes at least the combined magnitude of effect from each compound (additive) if not a multiplicative effect (synergistic) (Vandenberg 2023; Varshavsky 2023). Actual measurements of contaminants in the water system are limited and were not available for much of the exposed period. However, the ATSDR estimated historical exposures via modeling (ATSDR PHA 2017; Maslia 2008; Maslia 2013; Maslia expert report 2024). Again, the ATSDR utilized a reasonable, but conservative, approach with a simple additive effect in their analysis.

ATSDR water modeling is based on samples all obtained from 1980 or later (ATSDR PHA 2017). Estimates for water systems were constructed for the various water supply areas at Camp Lejeune.

Hadnot Point

- PCE: PCE contamination of at least 0.1 ppb was estimated beginning in the 1970s with a peak concentration of 39 ppb in 1983. The median exposure to PCE from April 1973-January 1985 was 14.5 ug/L*month and from 1975-1985 was 15.4 ug/L*month.
- TCE: TCE contamination of at least 0.1 ppb was estimated beginning in the 1950s with a peak concentration of 783 ppb in 1983. A measurement of 1400 ppb was measured in 1982. The median exposure to TCE from April 1973-January 1985 was 356.6 ug/L*month and from 1975-1985 was 365.9 ug/L*month.
- Benzene: Benzene contamination of at least 0.1 ppb was estimated beginning in the 1950s with a peak concentration of 12 ppb in 1984. A measurement of 2500 ppb was recorded in 1985. The median exposure to benzene from April 1973-January 1985 was 4.1 ug/L*month and from 1975-1985 was 4.6 ug/L*month.
- Vinyl Chloride: Vinyl chloride contamination of at least 0.1 ppb was estimated beginning in the 1970s with a peak concentration of 67 ppb in the early 1980s. The median exposure to vinyl chloride from April 1973-January 1985 was 20.3 ug/L*month and from 1975-1985 was 22.2 ug/L*month.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Tarawa Terrace

- PCE: PCE contamination of at least 0.1 ppb was estimated beginning in the 1950s with a peak concentration of 158 ppb in 1984. The median exposure to PCE from 1975-1985 was 84.9 ug/L*month.
- TCE: TCE contamination of at least 0.1 ppb was estimated beginning in the 1950s with a peak concentration of 7 ppb in the early 1980s. The median exposure to TCE from 1975-1985 was 3.5 ug/L*month.
- Vinyl Chloride: Vinyl chloride contamination of at least 0.1 ppb was estimated beginning in the 1950s with a peak concentration of 12 ppb in the early 1980s. The median exposure to vinyl chloride from 1975-1985 was 6.2 ug/L*month.

Holcomb Boulevard

- Prior to June 1972, water in this area was exclusively supplied from Hadnot Point. From 1972-1985, intermittent supplies from Hadnot Point were provided to this area. This resulted in modeled TCE maximum TCE contamination during the latter period of 23-66 ppb depending on the housing area. The maximum measured TCE concentration was 1148 ppb in 1985.

I have reviewed the ATSDR water modeling, the exhibits to Plaintiff's expert Morris Maslia, and his published reports, which are consistent (ATSDR PHA 2017; Maslia 2008; Maslia 2013; Maslia expert report 2024). The levels of these chemicals in the water at Camp Lejeune are hazardous to humans generally and also known to cause kidney cancer.

In addition to direct evidence from exposures at Camp Lejeune, the contributory body of human evidence includes occupational and environmental studies examining exposures to individual compounds of interest: PCE, TCE, benzene and vinyl chloride. These studies typically examine a single exposure in isolation. It is likely that outcomes following any single agent exposure identified in these studies represents an underestimated effect size for the cohort exposed at Camp Lejeune, as a combined exposure to the four compounds of interest is not suspected to be protective against any outcome studied. Consequently, if the literature on any individual compound is sufficient to meet the general causation standard applied to exposed individuals from Camp Lejeune, then studies directly examining the Camp Lejeune cohort is not required. Of note, TCE is almost unanimously recognized as a cause of kidney cancer in the scientific community and the EPA has proposed a total ban on the compound, as well as on PCE (EPA 2011, EPA 2023, IARC 2014). Further contributory evidence on specific compounds includes mechanistic and animal studies of individual chemicals.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Outcome of interest

The outcome of interest in this analysis consists of development of kidney cancers following exposure to the Camp Lejeune water system. Of note, some studies include urothelial/renal pelvis cancers with kidney cancers while some exclude them. Although more similar histologically to bladder tumors, most authors that do not separately analyze urothelial tumors include them with kidney cancers, and the measures of association in studies that include urothelial/renal pelvis cancers are similar to studies that do not include urothelial cancers (see appendix 1: table). Furthermore, in studies that directly compare urothelial/renal pelvis cancers to other kidney cancers, the measures of association are similar (Lynge 1997; Raaschou-Nielsen 2003). Urothelial/renal pelvis cancers occur in the kidney. The kidney cancer epidemiological studies apply for purposes of this causation analysis. All four of the toxins at issue cause upper tract urothelial carcinoma.

Studies of the Camp Lejeune population and/or those with elevated measures of association are abstracted in the attached appendix (see appendix 1: table).

Searches Performed

The literature was systematically searched utilizing Pubmed and Google Scholar for electronic searches. Search terms included combinations of each exposure (Camp Lejeune, TCE/trichloroethylene, perchloroethylene/tetrachloroethylene/PCE, benzene, and vinyl chloride) with “kidney cancer”. Full text articles with relevant abstracts were reviewed. Additionally, pertinent agency reports were examined. Potentially contributory articles contained in reference lists from agency reports and peer reviewed journal articles that were not included in the original search were also evaluated.

V Summary of Opinions

All opinions expressed herein are held to a reasonable degree of scientific certainty. Below is a summary of my opinions:

i. Direct epidemiological data provides compelling evidence that is sufficient to conclude that exposure to the Camp Lejeune water system causes kidney cancer.
ii. Epidemiological data provides compelling evidence that is sufficient to conclude that exposure to TCE causes kidney cancer.
iii. Epidemiological data provides compelling evidence that is sufficient to conclude that exposure to PCE causes kidney cancer.
iv. Epidemiological data provides substantial evidence that it is at least as likely as not that exposure to benzene causes kidney cancer.
v. Epidemiological data provides substantial evidence that it is at least as likely as not that exposure to vinyl chloride causes kidney cancer.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

vi. Exposure to a mixture of PCE, TCE, benzene, and vinyl chloride is not health protective but instead would have either an additive or synergistic harmful effect.
vii. Lower exposures may be conservatively and accurately represented by the least intense exposure demonstrating an elevated measure of association directly assessed in the population of interest. For kidney cancer following Camp Lejeune water exposures, the least intense exposures are greater than 1 to 4600 ug/L*month TVOC or 1 to 5 quarters on base at Camp Lejeune. This does not mean that exposure levels lower than these lower bounds are not causally related to kidney cancer. Furthermore, there are additional levels of exposure causally related to kidney cancer that are reported in the scientific literature as detailed in this report.

VI Discussion of Opinions

Epidemiology

Cohort studies provide the highest potential level of information regarding risks following exposure in a population. In these studies, an exposure is determined at a point in time and subjects are followed to monitor for the development of outcomes of interest. Cohort studies form the primary basis for assessing risk on a population level. Case control studies provide additional information on specific risk factors for an outcome of interest. However, they are necessarily backwards looking meaning that assessment of risk on a population level may not be as accurate. Nevertheless, for rare conditions such as cancers, case control studies can be of great benefit particularly in clarifying risk factors and identifying an exposure response relationship. Consequently, while informative, conclusions from such studies often are considered in combination with outcomes from cohort studies in bolstering causation determinations rather than providing sufficient evidence of causation alone. When available, meta-analyses combine the subjects in individual studies to provide more certainty around a pooled measure of association. Such an analysis is particularly robust and weighed heavily when assessing causation.

Finally, only studies with exposures to the Camp Lejeune water system or individual culprit compounds (TCE, PCE, benzene, or vinyl chloride) and an outcome of kidney cancer are reviewed below. Of note, this excludes the larger body of general dry-cleaning solvent and degreasing exposures that do not isolate culprit compounds of interest unless occupational classification is specific enough to serve as a proxy for a culprit compound exposure in the population studied. For example, an analysis of a cohort of dry-cleaning workers stratified by year of joining the union allowed employment to serve as a proxy given that after 1960 PCE was the exclusive solvent encountered (Blair 2003). However, in an earlier analysis of cohort, time stratification did not occur precluding any analysis of employment as a proxy for exclusive PCE exposure meaning this study was not included (Blair 1990). Importantly, excluding such general employment exposure categories does not impact the conclusions of the analysis.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Exposed soldiers and civilian personnel at Camp Lejeune typically experienced multiple routes of exposure, were exposed more continuously than occupational exposures that make up the bulk of the single agent literature bases and include in utero/childhood exposures which are less common than for worker studies. Given that exposures at Camp Lejeune involved multiple compounds each of which meets the equipoise and above standard for an association with kidney cancer, isolating a single compound of interest and using reported exposures solely for that compound as an estimate of kidney cancer risk in a mixed exposure such as Camp Lejeune will severely underestimate the risk associated with exposures on base. Therefore, direct examination of the population of interest at Camp Lejeune, utilizing exposure measurements that either combine culprit exposures into a summary metric or measure duration on base as an alternative quantification of mixed exposures are the most relevant analyses to fully incorporate the nature of the exposure. Nevertheless, if the body of literature on an individual culprit exposure analyzed separately meets the equipoise and above standard for causation, that necessarily means combined exposures that include such an exposure provides compelling evidence of causation, such as occurred at Camp Lejeune. Examination of comprehensive exposures at Camp Lejeune followed by each compound of interest occurs in the following sections. By convention, these studies are presented in chronological order, clustered by cohort. Such an order of description allows the reader to follow the progression of scientific inquiry.

Exposure: Camp Lejeune Water

Five human studies conducted by the ATSDR directly addressed the question of exposures to drinking water at Camp Lejeune and the outcome of kidney cancer. These five studies alone provide compelling evidence to meet the at least “as likely as not” standard. They also most directly examine the actual real-world exposures encountered at Camp Lejeune, inherently accounting for any degree of synergy that accompanies the combination of multiple water system contaminants. Additionally, as many constituent contaminant studies represent occupational exposures, these are unlikely to represent the same character of exposure as Camp Lejeune residents who both lived and worked on site, bathing in, inhaling, and consuming contaminated water.

The first study that examined mortality in a cohort of Marine and Naval personnel stationed at Camp Lejeune in the years 1975-1985 compared to Marine and Naval personnel stationed at Camp Pendleton (Bove 2014a). In an adjusted analysis with a 10-year lag, the HR for kidney cancer in Camp Lejeune personnel was 1.35. Further strengthening confidence in the conclusions, when a sensitivity analysis was performed that divided the Camp Lejeune cohort into a no/very low cumulative exposure group and a low/medium/high cumulative exposure group with Camp Pendleton remaining as the reference group, those with no/very low cumulative exposures had HRs ≤ 1.00 with all of the elevation in risk occurring among those with at least low cumulative exposures (HR 1.50). Additionally, there was a monotonic exposure-response trend for degrees of exposure to TVOC (the combination of PCE, TCE, trans-1,2-dichloroethylene, vinyl chloride and benzene) with a HR of 1.53 in the highest exposure group.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

A parallel analysis was performed examining mortality in a cohort of civilian employees at Camp Lejeune in the years 1973-1985 compared to civilian employees stationed at Camp Pendleton (Bove 2014b). In an adjusted analysis with a 10-year lag, the HR for kidney cancer in Camp Lejeune personnel was 1.92. All kidney cancer deaths among the Camp Lejeune cohort had cumulative exposures above the median for TVOC, with a HR for greater than median TVOC exposure of 4.44. Of note, this is a relatively young population, so mortality studies are unlikely to be a sensitive indicator of elevated measures of association in the population at large and may underestimate the effect size (Bove deposition 2024; Jones 2024).

Following these mortality studies, the ATSDR conducted a morbidity study focusing on kidney cancer diagnosis in former Marines, their families, and former base employees compared to former Camp Pendleton residents (ATSDR 2018). Case finding methodology utilized a survey with limited response rate making it difficult to fully exclude bias in the primary, unlagged analysis. However, measures of association were similar to other reports with a HR for kidney cancer of 1.52 in civilian employees and 1.31 in Marines. A series of nested case control studies within respondents were then performed. These demonstrated monotonic exposure-response relationships for combined TCE and PCE exposures with an OR of 1.80 in medium exposures and OR of 13.92 in high exposures in Camp Lejeune civilian employees compared to Camp Pendleton. In an internal analysis of Camp Lejeune civilian employees, there was a statistically significant relationship where medium exposures had an OR of 5.34 while high exposures had an OR of 41.54.

A recent publication examined kidney cancer incidence in a cohort of Marine and Naval personnel stationed at Camp Lejeune in the years 1975-1985 compared to Marine and Naval personnel stationed at Camp Pendleton, as well as in a cohort of civilian employees at Camp Lejeune in the years 1972-1985 compared to civilian employees stationed at Camp Pendleton (Bove 2024a). In an adjusted analysis, kidney cancer incidence demonstrated an overall elevated measure of association in civilian personnel (aHR 1.12) but not military personnel (aHR 1.06). A monotonic exposure-response for duration of exposure in civilian personnel was identified in those with a high duration of exposure (HR 1.70). A non-monotonic exposure-response was also identified in military personnel.

Finally, a follow-up mortality study to the paired studies from 2014 was recently published that included separate analyses of both civilian and military personnel formerly stationed at Camp Lejeune compared to Camp Pendleton (Bove 2024b). In an adjusted model with a 10-year lag, the aHR for kidney cancer deaths was 1.44 in civilian personnel and 1.21 in military personnel. A monotonic exposure-response for duration of exposure in civilian personnel was identified with a HR of 1.68 in those with a high duration of exposure. A non-monotonic exposure-response was also identified in military personnel.

Toxicology Associates, Prof. LLC
Dedicated to Patient Care, Research, and Teaching in Medical Toxicology

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Bradford Hill: Camp Lejeune Water

An elevated measure of association between Camp Lejeune water system exposure and kidney cancer has been identified in multiple studies (ATSDR 2018; Bove 2014a; Bove 2014b; Bove 2024a; Bove 2024b). The following discussion evaluates the evidence in order to determine whether it is "as likely as not" that this demonstrated association is causal.

Of note, I reviewed the later-discussed studies and publications regarding the Camp Lejeune chemicals prior to engaging in the Bradford Hill analysis for Camp Lejeune water, finding sufficient evidence for an association with each individual toxin. The inclusion of the Bradford Hill analysis for Camp Lejeune water as the exposure of interest before discussing the studies and publications regarding PCE, TCE, benzene, and vinyl chloride is purely for organizational purposes.

Strength of Association: Multiple studies demonstrate elevated measures of association (ATSDR 2018; Bove 2014a; Bove 2014b; Bove 2024a; Bove 2024b). These range up to a HR of 1.92 for military personnel or their families stationed at Camp Lejeune or civilian employees on base (Bove 2014b). Furthermore, any exposure misclassification would likely serve to attenuate the measure of association, biasing toward the null (Bove Deposition 2024). This assessment comports with current scientific, toxicological and epidemiological knowledge. Consequently, the range of associations reported represent a minimum estimate of the true association. This analysis provides direct evidence that exposure to the Camp Lejeune water system is a cause of kidney cancer given the demonstrated **strength of association** in the epidemiologic literature.

Consistency: Individual studies of both civilian (ATSDR 2018; Bove 2014b; Bove 2024a; Bove 2024b) and military personnel (ATSDR 2018; Bove 2014a; Bove 2024b) provide consistent findings of an association in distinct populations between time at Camp Lejeune and kidney cancer. Additionally, analysis of both cancer diagnosis (ATSDR 2018; Bove 2024a) and cancer mortality (Bove 2014a; Bove 2014b; Bove 2024b) as the outcome demonstrate similar results. Furthermore, both cohort (Bove 2014b; Bove 2024a; Bove 2024b) and case-control (ATSDR 2018) studies reach similar conclusions. Such a variety of studies provide **consistent** evidence that exposure to the Camp Lejeune water system is a cause of kidney cancer.

Exposure-Response: Monotonic exposure-response relationships have been demonstrated for increased TVOC exposure (Bove 2014a; Bove 2014b), combined TCE and PCE exposure (ATSDR 2018), and duration at Camp Lejeune (Bove 2024a; Bove 2024b). Similar results despite varied methods of assessing exposure provide compelling evidence of causation given the **exposure-response** relationship demonstrated in multiple studies.

Temporality: Multiple studies utilized 10-year lags to ensure that exposure to Camp Lejeune water occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

of interest (Bove 2014a; Bove 2014b; Bove 2024a). Two of these studies even conducted sensitivity analyses with up to 20-year lags without substantive changes in results (Bove 2014a; Bove 2014b). Such study design provides evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

Biological Plausibility: Exposure to Camp Lejeune water follows a clear biologically plausible pathway for causation of kidney cancer. As discussed in subsequent sections, TCE, PCE, vinyl chloride, and benzene are all contaminants of the Camp Lejeune systems, and all meet the "as likely as not" standard as a cause of kidney cancer. They each have a biologically plausible mechanism of action to cause kidney cancer. TCE and PCE have the most robust literature base for evidence of causation of kidney cancer, including the most literature on a known mechanism of action. The glutathione conjugation metabolic pathway has been implicated for both TCE and PCE with confirmation in humans (Moore 2010). Due to a lack of investigation, a distinct mechanism of action to cause kidney cancer following vinyl chloride and benzene exposure has not been established in the published research. However, both toxins have been established as carcinogens with plausible mechanisms for causation of kidney cancer. The body of evidence provides clear support for **biologically plausible** pathways from Camp Lejeune water exposure to development of kidney cancer.

Analogy: Camp Lejeune water exposure is directly analogous to exposures in two other water systems. These involved single agent contamination, with both TCE (Andrew 2022) and PCE (Aschengrau 1993) demonstrating elevated measures of association with kidney cancer. Additionally, studies of multiple occupational and environmental exposures involving TCE, PCE, vinyl chloride, or benzene provide additional evidence of elevated measures of association with kidney cancer. This **analogous** evidence of causation is discussed in detail in the agent specific sections of this report.

Experiment: There is no human **experimental** evidence of causation involving Camp Lejeune water exposure and kidney cancer. An absence of experimental data is common when considering the body of evidence surrounding occupational or environmental toxins. Of note, a lack of relevant experimental studies does not provide evidence against causation.

Specificity: There are multiple possible causes of kidney cancer and multiple types of kidney cancer that were contained in each analysis of Camp Lejeune water limiting the contribution of **specificity** to causation.

Coherence: The human, animal, and mechanistic literature provides a robust and **coherent** body of evidence for Camp Lejeune water exposure as a cause of kidney cancer. There is no substantial contrary data suggesting an alternative explanation for the observed measures of association.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Summary: Camp Lejeune Water

The evidence surrounding Camp Lejeune water exposures and the outcome of kidney cancer discussed above is compelling. Given the weight of evidence presented in the Bradford Hill analysis, not only is the at least "as likely as" standard met, but there is also sufficient evidence to establish causation of kidney cancer using a "more likely than not" standard.

Additionally, the 2017 ATSDR framework is also clearly exceeded:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence."

In this case, multiple high utility epidemiological studies have been performed and demonstrate consistently elevated measures of association, well in excess of the conservative criteria set forth by ATSDR. It is evident that exposure to Camp Lejeune water is not only at least as likely as not a cause of kidney cancer but also that there is sufficient evidence to establish Camp Lejeune water exposure as a cause of kidney cancer.

<u>Exposure: TCE</u>

Cohort Studies

Hill Air Force Base, Utah (NCI)

An initial cohort study of civilian employees working at Hill Air Force Base in Utah did not find an association between TCE exposure and kidney cancer in white workers (SMR 0.83) on initial analysis (Spirtas 1991). However, with longer follow up of this cohort, the risk of kidney cancer was found to be elevated (RR 1.6) although there was no exposure-response relationship (Blair 1998). An elevated measure of association (HR 1.18) remained upon reanalysis with additional follow up (Radican 2008).

TCE Production Workers, Sweden

A cohort study of Swedish workers exposed to TCE found an elevated measure of association (SIR 1.16) with kidney cancer in males. (Axelson 1994).

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

TCE Production Workers, Finland

A cohort study of Finnish workers exposed to TCE did not find an association with kidney cancer in the overall cohort (SIR 0.87), although there was an elevated measure of association (SIR 1.39) in those followed for 10-19 years (Anttila 1995).

German Cardboard Factory Workers

The first well conducted cohort epidemiology study that found a statistically significantly elevated risk of developing kidney cancer (SIR 7.97) and death from kidney cancer (SMR 3.28) was of German cardboard factory workers exposed to TCE for at least 1 year between 1956 and 1975 with an average latency of 28 years (Henschler 1995).

Aerospace Workers, Hughes Aircraft, Arizona

In this cohort study, an elevated measure of association between the TCE exposed group and kidney cancer (SMR 1.32) was observed (Morgan 1998). The excess was seen in the high exposure group (SMR 1.78; RR 1.59) but not the low exposure group (SMR 0.47; RR 0.31) and the peak medium and high exposure group compared to the low and no exposure group (RR 1.89).

Aircraft Manufacturing Workers, Lockheed Martin, California

Aircraft manufacturing workers employed for at least one year after 1960 at the Lockheed Martin Skunk Works were included in a cohort study that revealed no excess kidney cancer deaths (SMR 0.99) associated with TCE exposure (Boice 1999). A follow up analysis of workers employed for at least one year 1960-1996 followed through 1998 likewise did not demonstrate an association (SMR 0.66) with kidney cancer deaths (Lipworth 2011).

Uranium Processing Workers, Fernald Feed, Ohio

A cohort study of uranium processing workers found no association between TCE exposure and kidney cancer (Ritz 1999).

TCE Exposed Workers, Denmark

A cohort study of Danish workers found an elevated measure of association (SIR 1.1) between TCE exposure and kidney cancer (Hansen 2001). The association differed between women (SIR 2.4) and men (SIR 0.9). An elevated measure of association (SIR 1.2) was also seen on subsequent analysis with up to a 20-year lag (Raaschou-Nielsen 2003). Additionally, in a sub-cohort analysis of highly exposed workers who also demonstrated an elevated measure (SIR 1.4), the SIRs increased with increasing lag time, increasing duration of employment, and earlier year of first employment.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Electronic Factory Workers, Taiwan

A cohort study of Taiwanese electronic factory workers found no cases of kidney cancer in a TCE exposed population of male workers with "various latencies" (Chang 2003). However, the analysis did reveal an elevated risk of kidney cancer in females (SMR 1.18) with no dose-response relationship in the entire cohort.

Rocketdyne Worker Study, Santa Susana Field Laboratory, California

A cohort study of aerospace employees engaged in rocket testing with lags up to 20 years revealed a statistically significant association (RR 4.90) between high levels of TCE exposure and kidney cancer incidence as well as a statistically significant dose response with elevated association (RR 1.87) between medium levels of TCE exposure and kidney cancer incidence (Zhao 2005). Additionally, kidney cancer mortality demonstrated a monotonic dose response with elevated measure of association between both medium (RR 1.43) and high (RR 2.03) levels of TCE exposure in this cohort. A similar elevated measure of association (SMR 2.22) with kidney cancer death was seen in a separate analysis utilizing up to a 10-year lag of Test Stand Mechanics with duties consisting of potential exposure to TCE (Boice 2006). Increased exposures as measured by years of exposure and number of engine flushes were both associated with kidney cancer.

Nordic Occupational Cancer Study, Denmark, Finland, Iceland, Norway and Sweden

No elevated measures of association (HR 1.00-1.02) were seen in a large Nordic cohort study, although the number of TCE exposed subjects was limited (Vlaanderen 2013). However, when stratified by sex, the 2nd tertile in women demonstrated an elevated measure of association (HR 1.12).

Camp Lejeune

An elevated measure of association (HR 1.50) for kidney cancer deaths was identified in a 10-year lagged analysis of military personnel stationed at Camp Lejeune compared to Camp Pendleton with at least low exposure to TCE (Bove 2014a). In a similar analysis of civilian personnel, all kidney cancer deaths were exposed to greater than the median TCE exposure, although the numbers were too small to calculate a measure of association (Bove 2014b).

Microelectronics and Business Machine Facility Workers, New York State

In a regression analysis, an elevated measure of association (HR 1.24) was identified at 5 modified exposure years for TCE with a 10-year lag (Silver 2014). However, the regression analysis was not the primary analysis in this cohort study.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Railroad Workers, Norway

A statistically significantly elevated measure of association (SIR 1.7) between TCE exposure and development of kidney cancer was observed in this cohort (Buhagen 2016). The authors state, "The present study supports the view that TCE is a kidney carcinogen."

Case Control Studies

Transformer Manufacturing Workers, General Electric, Massachusetts

Compared to matched non-cancer deaths from the same worker cohort, no elevated measure of association (OR 0.99) between TCE and kidney cancer was seen (Greenland 1994).

Cardboard Factory Workers, Germany

A follow up case control study to Henschler's 1995 cohort study identified a statistically significant elevated measure of association between long term TCE exposure and renal cell cancer (adjusted OR 10.8) with an average latency of 33 years and a statistically significant exposure-response (Vamvakas 1998). A monotonic dose response was evident with OR for high exposure to TCE of 11.42. Another follow-up study with lags up to 20 years demonstrated a statistically significant elevated measure of association (OR 2.47) in TCE exposed workers, with increasingly elevated measures in those reporting narcotic symptoms both at any time (OR 3.71) and daily (5.91), concerning for higher risk with high peak exposures (Bruning 2003).

Occupational Organic Solvent Exposures, Minnesota

A study of renal cell carcinoma patients revealed an elevated measure of association (OR 1.3) with TCE exposure, one that was statistically significantly elevated in women (OR 1.96) but not men (OR 1.04) (Dosemeci 1999).

Occupational TCE Exposures, East and West Germany

A population matched study of renal cell carcinoma cases demonstrated recurrently elevated measures of association in males (OR 1.1-1.3) depending on the degree of exposure to TCE and method of estimating exposure (Pesch 2000). Measures of association for more varied in females (OR 0.8-1.8) although no exposure response was evident in either sex.

Occupational TCE Exposures, France

A well conducted population matched study of renal cell carcinoma cases with sophisticated analysis demonstrated an elevated measure of association (aOR 1.64) for all exposed (Charbotel 2006). Statistically significant elevated measures of association were identified for a high cumulative dose of

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

TCE (aOR 2.16) as well as high+peak exposures (aOR 2.73), with a monotonic exposure response effect. This study forms the basis for the EPA's dose extrapolation in kidney cancer risk modeling for TCE.

Central and Eastern European Renal Cell Cancer Study, Czech Republic, Poland, Romania, and Russia

Another well conducted population matched study of renal carcinoma with a 20-year lag also demonstrated a statistically significant elevated measure of association (OR 1.63) for TCE exposed individuals (Moore 2010). Additionally, a statistically significant dose-response was identified, with those above the median TCE exposure having an even higher measure (OR 2.34). Further genetic analysis was performed with statistically significant association found in TCE exposed subjects with at least one intact GSTT1 allele (OR 1.88), but not among subjects with two deleted alleles (OR 0.93). A follow up analysis examined the association between TCE exposure and subtypes of clear cell renal cell carcinoma, with clear cell B subtypes demonstrating a statistically significant elevated measure of association (OR 3.09) while clear cell A subtypes had an elevated measure of association (OR 1.25) that was not statistically significant (Purdue 2021).

Chemical Plant Workers, Montreal, Canada

A population matched case control study examining various occupational chlorinated solvent exposures and various cancers failed to find an association (OR 1.0) between TCE exposure and kidney cancer (Christensen 2013).

Camp Lejeune

In a series of nested case control studies performed by ATSDR, a monotonic exposure response relationship was identified when comparing Marines stationed at Camp Lejeune to those at Camp Pendleton (ATSDR 2018). Both medium (OR 1.33) and high (OR 1.42) exposures to TCE demonstrated elevated measures of exposure. In an internal analysis of Camp Lejeune Marines, a statistically significant monotonic exposure response was identified with medium (OR 1.45) and high (OR 1.55) exposures to TCE also with elevated measures of association.

US Kidney Cancer Study, Chicago, Illinois and Detroit, Michigan

A population matched case control study with sophisticated analysis failed to identify an association (OR 0.8) between overall TCE exposure and kidney cancer (Purdue 2017). However, an elevated measure of association was seen in those high intensity TCE exposures with at least 6 hours of weekly exposure (OR 2.0) and those with at least 1560 cumulative hours exposed (OR 1.7).

Groundwater TCE Contamination, New Hampshire

A temporo-spatial health system matched case control study examined the association between degree of estimated groundwater contamination and kidney cancer in New Hampshire with up to 15-year lags

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

(Andrew 2022). The authors found a statistically significant association between the 50-75% 15-year median TCE exposure and kidney cancer (OR 1.78) but not in the highest quartile (OR 0.92). The authors theorized that misclassification bias or more focused remediation at higher exposed sites may have been the cause of this lack of exposure-response relationship.

Meta-analyses

The first meta-analysis included the following cohorts: Hill Air Force Base, Utah (NCI), Swedish TCE Production Workers, Finnish TCE Production Workers, and Aerospace Workers, Hughs Aircraft, Arizona (Morgan 1998). The meta-SMR was 1.09, although only the initial follow up period for the Hill Air Force Base cohort was included (Spirtas 1991) rather than the updated follow up (Blair 1998).

A subsequent comprehensive meta-analysis included 23 studies: 16 cohort and 7 case-control (Kelsh 2010). This analysis demonstrated statistically significantly elevated measures of association across all studies (RR 1.42), after removal of 3 outlier studies (RR 1.24), in only cohort studies (RR 1.34), and in only cohort studies with well documented exposure assessment (RR 1.34).

Similarly, a meta-analysis of 15 studies: 9 cohort and 5 case-control again found statistically significantly elevated measures of association for TCE exposure (RRm 1.27) with a higher measure (RRm 1.58) with higher TCE exposure (Scott 2011). The authors state, “Our findings provide strong support for a causal association between TCE exposure and kidney cancer.”

Another updated meta-analysis of 28 studies: 15 cohort and 13 case-control studies also came to similar conclusions (Karami 2012). Statistically significantly elevated measures of association were identified for studies where TCE exposure was explicitly identified in cohort (RR 1.26), case-control (RR 1.35), and all studies (RR 1.32). The authors state, “This updated meta-analysis supports an association between occupational TCE exposure and kidney cancer.”

Pooling of three TCE exposed worker cohorts from Sweden, Denmark, and Finland did not demonstrate (SIR 1.01) an elevated measure of association with lags up to 20 years (Hansen 2013). However, when analyzed by urine TCA levels, the highest exposure group demonstrated an elevated measure of association (aHRR 2.04).

Bradford Hill: TCE

An association between TCE exposure and kidney cancer has been identified in multiple studies including occupational exposures, non-Camp Lejeune water system exposures, and Camp Lejeune water system exposures. The following discussion evaluates the evidence to determine whether it is “as likely as not” that this demonstrated association is causal.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Strength of Association: Many studies demonstrate elevated measures of association (ATSDR 2018; Axelson 1994; Blair 1998; Boice 2006, Bove 2014a; Bruning 2003; Buhagen 2016; Charbotel 2006; Dosemeci 1999; Henschler 1995; Morgan 1998; Moore 2010; Raaschou-Nielsen 2003; Radican 2008; Vamvakas 1998; Zhao 2005). These range up to an aOR of 10.8 (Vamvakas 1998). Multiple meta-analyses have identified an elevated measures of association ranging from mRR 1.27 to mRR 1.42, providing a realistic estimate of the true population risk of kidney cancer following exposure to TCE (Karami 2012; Kelsh 2010; Scott 2011). This body of literature provides strong evidence that exposure to TCE is a cause of kidney cancer given the demonstrated **strength of association** in the epidemiologic literature.

Consistency: Individual studies of largely inhalational occupational exposures (Axelson 1994; Blair 1998; Boice 2006; Bruning 2003; Buhagen 2016; Charbotel 2006; Dosemeci 1999; Henschler 1995; Moore 2010; Morgan 1998; Radican 2008; Raaschou-Nielsen 2003; Vamvakas 1998; Vlaanderen 2013; Zhao 2005) and water system contamination (Andrew 2022; ATSDR 2018; Bove 2014a; Bove 2014b) have been conducted, examining a variety of routes of exposure in multiple countries throughout the world provide consistent findings of an association in distinct populations between TCE exposure and kidney cancer. Additionally, analysis of both cancer diagnosis (ATSDR 2018; Bruning 2003; Buhagen 2016; Charbotel 2006; Dosemeci 1999; Henschler 1995; Moore 2010; Raaschou-Nielsen 2003; Vamvakas 1998; Vlaanderen 2013; Zhao 2005) and cancer mortality (Axelson 1994; Blair 1998; Boice 2006; Bove 2014a; Bove 2014b; Henschler 1995; Morgan 1998; Radican 2008) as the outcome demonstrate similar results. Furthermore, both cohort (Axelson 1994; Blair 1998; Boice 2006; Bove 2014a; Bove 2014b; Buhagen 2016; Henschler 1995; Morgan 1998; Radican 2008; Raaschou-Nielsen 2003; Vlaanderen 2013; Zhao 2005) and case-control (ATSDR 2018; Bruning 2003; Charbotel 2006; Dosemeci 1999; Moore 2010; Vamvakas 1998) studies reach nearly identical conclusions. Many of these studies have been pooled in meta-analyses (Hansen 2013; Karami 2012; Kelsh 2010; Scott 2011). Such a variety of studies by a multitude of investigators all reaching similar results provide **consistent** evidence that exposure to TCE is a cause of kidney cancer.

Exposure-Response: Multiple studies have demonstrated monotonic exposure-response for increased intensity of TCE exposure with increased kidney cancer (ATSDR 2018; Charbotel 2006; Kelsh 2010; Moore 2010; Vamvakas 1998; Zhao 2005). Additional evidence of exposure-response occurs with other measures of intensity of exposure (Boice 2006; Bruning 2003; Hansen 2013; Morgan 1998; Purdue 2017; Raaschou-Nielsen 2003; Scott 2011; Vlaanderen 2013). Similar results despite varied methods of assessing exposure provide compelling evidence of causation given the **exposure-response** relationship demonstrated in multiple studies.

Temporality: Multiple studies utilized prolonged lags to ensure that exposure to TCE occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome of interest (Andrew 2022; Boice 2006; Bove 2014a; Bove 2014b; Bruning 2003; Hansen 2013; Moore 2010; Purdue

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

2017; Raaschou-Nielsen 2003; Radican 2008; Vlaanderen 2013; Zhao 2005). Other studies reported prolonged latency periods or follow up times (Anttila 1995; Chang 2003; Henschler 1995; Vamvakas 1998). Such study designs provide evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

Biological Plausibility: Exposure to TCE follows a clear biologically plausible pathway for causation of kidney cancer. As discussed in detail in subsequent sections, laboratory studies have implicated the glutathione conjugation metabolic pathway for TCE as the causal mechanism of kidney cancer with confirmation of this pathway in humans (Moore 2010). This provides clear support for a **biologically plausible** pathway from TCE exposure to development of kidney cancer.

Analogy: TCE exposure is analogous to PCE exposure, with similarly elevated measures of association and an identical biological causal pathway. This **analogous** evidence of PCE as a cause of kidney cancer is discussed in detail in the following section.

Experiment: There is no human **experimental** evidence of causation involving TCE and kidney cancer.

An absence of experimental data is common when considering the body of evidence surrounding occupational or environmental toxins. Of note, a lack of relevant experimental studies does not provide evidence against causation.

Specificity: A specific mechanism of causation has been identified in humans with TCE exposure only in those with an intact glutathione pathway (Moore 2010). There is a study of clear cell tumors with B subtypes demonstrating higher measures of association than A subtypes (Purdue 2021). Additionally, TCE exposure has been identified with higher measures of association for kidney cancer in women rather than men (Chang 2003; Dosemeci 1999; Hansen 2001; Pesch 2000; Vlaanderen 2013). However, it is unclear if this represents differences in exposure assessments or a true sex difference in susceptibility to kidney cancer. There is clear evidence of **specificity** of mechanism for TCE exposure to cause kidney cancer. It is also possible that female gender and Type B clear cell cancers may be more related to TCE exposures although evidence is limited.

Coherence: The human, animal, and mechanistic literature provides a robust and **coherent** body of evidence for TCE exposure as a cause of kidney cancer. There is no substantial contrary data suggesting an alternative explanation for the observed measures of association.

Summary: TCE

The evidence surrounding TCE exposures and the outcome of kidney cancer discussed above is compelling. Given the weight of evidence presented in the Bradford Hill analysis, not only is the at least

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

"as likely as" standard met, but there is also sufficient evidence to establish causation of kidney cancer using a "more likely than not" standard.

Additionally, the 2017 ATSDR framework is also clearly exceeded:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

A meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, i.e., ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence."

In this case, multiple meta-analyses demonstrate risk estimates with elevated measures of association, well in excess of the criteria set forth by ATSDR. The weight of evidence indicates that TCE is not only at least as likely as not a cause of kidney cancer but also that there is sufficient evidence to establish TCE exposure as a cause of kidney cancer.

<u>Exposure: PCE</u>

Cohort Studies

TCE Production Workers, Finland

A cohort study of Finnish workers exposed to PCE demonstrated an elevated measure of association (SIR 1.82) with kidney cancer in the overall cohort with a mean length of follow up of 18 years (Anttila 1995).

Aircraft Manufacturing Workers, Lockheed Martin, California

Aircraft manufacturing workers employed for at least one year after 1960 at the Lockheed Martin Skunk Works were included in a cohort study that revealed no excess kidney cancer deaths (SMR 0.69) associated with PCE exposure (Boice 1999). A follow up analysis of workers employed for at least one year 1960-1996 followed through 1998 likewise did not demonstrate an association (SMR 0.80) with kidney cancer deaths (Lipworth 2011).

Dry Cleaning Workers, United States

An elevated measure of association (SMR 1.41) for kidney cancer mortality was reported in a cohort study of dry cleaner union members who worked in PCE exposed shops for at least a year prior to 1960 with up to 20-year lags (Ruder 2001). An elevated measure of association (SMR 1.73) was also observed

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

when the analysis was restricted to workers who only worked in shops with PCE exposures and without potential for alternative solvent exposures. A subsequent report continued to demonstrate elevated measures of association in the entire cohort (SMR 1.14) and in the PCE only group (SMR 1.35) with additional follow up (Calvert 2011).

Dry Cleaner Union Members, St Louis, Missouri

A follow up study of a cohort of dry cleaner union members with estimated solvent exposure stratification was performed (Blair 2003). When the analysis was restricted to workers who joined the union after 1960, the period when PCE became the predominant solvent in the industry, no elevated measure of association (SMR 0.7) was identified. However, additional follow-up then demonstrated an elevated measure of association (SMR 1.8) in those who joined after 1960 but not before (SMR 1.1), suggesting a PCE specific effect (Callahan 2019). Additionally, a statistically significant dose response for degree of exposure (high exposure=HR 24.4) was seen with 10 year and 20-year lags but not with an unlagged analysis.

Nordic Dry Cleaners and Laundry Workers, Denmark, Norway, Sweden, and Finland

Employment as a dry cleaner in 1970 was used as a proxy for PCE exposure in this cohort given the near exclusive use of the compound in that capacity and ubiquitous exposure in the industry (Lynge 2006). However, the measure of association (RR 0.67) was not elevated in this cohort.

Nordic Occupational Cancer Study, Denmark, Finland, Iceland, Norway and Sweden

An elevated measure of association (HR 1.11) in the first tertile of exposure was seen in a large Nordic cohort study, although the number of PCE exposed subjects was limited (Vlaanderen 2013). Additionally, when stratified by sex, only the first tertile in men demonstrated an elevated measure of association (HR 1.14).

Microelectronics and Business Machine Facility Workers, New York State

In a regression analysis, no association (HR 0.15) was identified at 5 modified exposure years for PCE (Silver 2014). However, the regression analysis was not the primary analysis in this cohort study.

Camp Lejeune

An elevated measure of association (HR 1.55) for kidney cancer deaths was identified in a 10-year lagged analysis of military personnel stationed at Camp Lejeune compared to Camp Pendleton with at least low exposure to PCE (Bove 2014a). Elevated measures of association were identified for all levels of exposure although the exposure response relationship was nonmonotonic. In a similar analysis of civilian personnel, all kidney cancer deaths were exposed to greater than the median PCE exposure, although the numbers were too small to calculate a measure of association (Bove 2014b).

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Case Control Studies

Water System Contamination, Massachusetts

Residents exposed to PCE via a contaminated water system, similar in nature of exposure to Camp Lejeune residents although limited to isolated system contamination with PCE rather than a multiple compounds, were matched to population-based controls in a well conducted study (Aschengrau 1993). Although the authors were not able conduct an analysis accounting for 15 years of latency due to limited cases of kidney cancer available, any PCE exposure (OR 1.23) and low PCE exposure (OR 1.36) demonstrated elevated measures of association with kidney cancer in an analysis not accounting for latency.

Occupational PCE Exposures, East and West Germany

A population matched study of renal cell carcinoma cases demonstrated recurrently elevated measures of association in males (OR 1.1-1.4) depending on the degree of exposure to PCE and method of estimating exposure (Pesch 2000). Measures of association varied in females (OR 0.7-2.2) although no dose-response was evident in either sex.

Chemical Plant Workers, Montreal, Canada

A population matched case control study with a 5-year lag examining various occupational chlorinated solvent exposures and various cancers as outcomes reported elevated measures of association between any (OR 1.6) and substantial (OR 3.1) PCE exposure and kidney cancer (Christensen 2013).

Camp Lejeune

In a series of nested case control studies performed by ATSDR, a monotonic exposure response relationship was identified when comparing Marines stationed at Camp Lejeune to those at Camp Pendleton (ATSDR 2018). Both medium (OR 1.28) and high (OR 1.79) exposures to PCE demonstrated elevated measures of exposure. In an internal analysis of Camp Lejeune Marines, a statistically significant monotonic exposure response was identified with medium (OR 1.43) and high (OR 2.01) exposures to PCE also with elevated measures of association.

US Kidney Cancer Study, Chicago, Illinois and Detroit, Michigan

A population matched case control study with sophisticated analysis identified a range of measures of association, some elevated (OR 0.9-1.2) between various probabilities of PCE exposure and kidney cancer (Purdue 2017). In more detailed analyses of those with high intensity PCE exposures, a statistically significant elevated measure of association was reported in those with at least 1820 cumulative hours (OR 3.1). Additionally, elevated measures of association were seen with at least 4 years of exposure (OR 1.4) and increasing hours of weekly exposure (OR 2.5 at 15 hours).

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Bradford Hill: PCE

An association between PCE exposure and kidney cancer has been identified in multiple studies including occupational exposures, non-Camp Lejeune water system exposures, and Camp Lejeune water system exposures. The following discussion evaluates the evidence to determine whether it is "as likely as not" that this demonstrated association is causal.

Strength of Association: Many studies demonstrate elevated measures of association between exposure to PCE and kidney cancer (Anttila 1995; Aschengrau 1993; ATSDR 2018; Bove 2014a; Callahan 2019; Calvert 2011; Christensen 2013; Purdue 2017; Ruder 2001; Vlaanderen 2013). These range up to an SIR of 1.82 (Anttila 1995). Such a body of literature provides strong evidence that exposure to PCE is a cause of kidney cancer given the demonstrated **strength of association** in the epidemiologic literature.

Consistency: Individual studies of largely inhalational occupational exposures (Anttila 1995, Callahan 2019, Calvert 2011, Christensen 2013; Pesch 2000; Purdue 2017; Ruder 2001; Vlaanderen 2013) and water system contamination resulting in a variety of routes of exposure (Aschengrau 1993; ATSDR 2018; Bove 2014a; Bove 2014b) in multiple countries throughout the world provide consistent findings of an association in distinct populations between PCE exposure and kidney cancer. Additionally, analysis of both cancer diagnosis (Anttila 1995; ATSDR 2018; Christensen 2013; Purdue 2017; Vlaanderen 2013) and cancer mortality (Aschengrau 1993; Bove 2014a; Bove 2014b; Callahan 2019; Calvert 2011; Ruder 2001) as the outcome demonstrate similar results. Furthermore, both cohort (Anttila 1995; Bove 2014a; Bove 2014b; Callahan 2019; Calvert 2011; Ruder 2001; Vlaanderen 2013) and case-control (Aschengrau 1993; ATSDR 2018; Christensen 2013; Purdue 2017) studies reach nearly identical conclusions. Such a variety of studies by a multitude of investigators all reaching similar results provide **consistent** evidence that exposure to PCE is a cause of kidney cancer.

Exposure-Response: Multiple studies have demonstrated monotonic exposure-response relationships for increased intensity of PCE exposure with increased kidney cancer (ATSDR 2018; Callahan 2019). Additional evidence of exposure-response occurs with other measures of intensity of exposure (Aschengrau 1993; Bove 2014a; Christensen 2013; Purdue 2017; Vlaanderen 2013). Similar results despite varied methods of assessing exposure provide compelling evidence of causation given the **exposure-response** relationship demonstrated in multiple studies.

Temporality: Multiple studies utilized prolonged lags to ensure that exposure to PCE occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome of interest (Bove 2014a; Bove 2014b; Callahan 2019; Calvert 2011; Christensen 2013; Ruder 2001; Vlaanderen 2013). Other studies reported prolonged latency periods or follow up times (Anttila 1995; Aschengrau 1993). Such study designs provide evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Biological Plausibility: Exposure to PCE follows the same biologically plausible pathway for causation of kidney cancer that has been established for TCE causing kidney cancer. As discussed in detail in subsequent sections, laboratory studies have implicated the glutathione conjugation metabolic pathway for PCE as the causal mechanism of kidney cancer in mechanistic and animal studies. This provides clear support for a **biologically plausible** pathway from PCE exposure to development of kidney cancer.

Analogy: PCE exposure is analogous to TCE exposure, with similarly elevated measures of association and an identical biological causal pathway. This **analogous** evidence of TCE as a cause of kidney cancer is discussed in detail in the prior section.

Experiment: There is no human **experimental** evidence of causation involving PCE and kidney cancer. An absence of experimental data is common when considering the body of evidence surrounding occupational or environmental toxins. Of note, a lack of relevant experimental studies does not provide evidence against causation.

Specificity: PCE exposure has been identified with a higher measure of association for kidney cancer in women in one study (Pesch 2000) and men in another (Vlaanderen 2013). However, it is not clear if these findings are due to differences in exposure assessment or true variations in susceptibility to kidney cancer by sex. There are multiple possible causes of kidney cancer and multiple types of kidney cancer that were contained in each analysis of PCE exposure and kidney cancer limiting **specificity** in contributing to causation.

Coherence: The human, animal, and mechanistic literature provides a robust and **coherent** body of evidence for PCE exposure as a cause of kidney cancer. There is no substantial contrary data suggesting an alternative explanation for the observed measures of association.

Summary: PCE

The evidence surrounding PCE exposures and the outcome of kidney cancer discussed above is compelling. Given the weight of evidence presented in the Bradford Hill analysis, not only is the at least "as likely as" standard met, but there is also sufficient evidence to establish causation of kidney cancer using a "more likely than not" standard.

Additionally, the 2017 ATSDR framework is also clearly met:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence."

In this case, multiple high utility epidemiological studies have been performed and demonstrate consistent risk estimates with elevated measures of association, well in excess of the conservative criteria set forth by ATSDR. It is evident that exposure to PCE is not only at least as likely as not a cause of kidney cancer but also that there is sufficient evidence to establish PCE exposure as a cause of kidney cancer.

Exposure: Benzene

Cohort Studies

Chemical Workers, United States

Chemical workers exposed to benzene continuously or intermittently as well as an unexposed group of workers were followed for mortality outcomes (Wong 1987a). The continuously exposed group exhibited an elevated measure of association (SMR 1.40) with kidney cancer deaths while the intermittent and unexposed groups failed to demonstrate an association. There was no exposure response evident in a complementary analysis (Wong 1987b)

Service Station Workers, Denmark, Finland, Norway, and Sweden

Service station workers with elevated estimated benzene exposures were followed for 15-20 years (Lynge 1997). For incidence of both kidney cancer (SIR 1.3) and renal pelvis cancer (SIR 2.0), male service station workers demonstrated statistically significant elevated measures of association. Female service station workers exhibited an elevated measure of association with kidney cancer (SIR 1.2).

Occupational Benzene Exposures, England and Wales

Workers exposed to benzene did not demonstrate an increase in kidney cancer incidence (SRR 0.90) or kidney cancer mortality (SRR 1.03) in a British cohort (Sorahan 2005)

Nordic Occupational Cancer Study, Denmark, Finland, Iceland, Norway and Sweden

No elevated measures of association were seen in a large Nordic cohort study at varying intensities of exposure (Vlaanderen 2013).

Camp Lejeune

An elevated measure of association (HR 1.48) for kidney cancer deaths was identified in a 10-year lagged analysis of military personnel stationed at Camp Lejeune compared to Camp Pendleton with at least low

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

exposure to benzene (Bove 2014a). Elevated measures of association were identified for all levels of exposure although the exposure response relationship was nonmonotonic. In a similar 10 year lagged analysis of civilian personnel, kidney cancer deaths were associated (HR 1.82) with a greater than median benzene exposure (Bove 2014b).

Dow Chemical Workers, Michigan

No elevated measure of association (SMR 0.72) with kidney cancer was seen in the cohort of benzene exposed chemical workers (Bond 1986). Likewise, no elevated measure of association (SMR 0.78) with kidney cancer was seen in the cohort of benzene exposed chemical workers on the most recent follow-up analysis (Collins 2015).

Case Control

Transformer Manufacturing Workers, General Electric, Massachusetts

Compared to matched non-cancer deaths from the same worker cohort, a statistically significant elevated measure of association (OR 4.29) between benzene exposure and kidney cancer was seen (Greenland 1994). Standard lag for the analysis was 2 years although various analysis included up to an 8-year latency. When analyzed as a continuous variable, an elevated measure of association (OR 1.9) was evident at the maximum likely exposure.

Occupational Exposures, Montreal, Canada

A population-based case control study utilizing “a reasonable period of latency” examining occupational exposures demonstrated a monotonic dose response with an elevated measure of association for both low (OR 1.2) and medium/high (OR 1.3) benzene exposures (Gerin 1998).

Occupational Benzene Exposures, East and West Germany

A population matched study of renal cell carcinoma cases demonstrated recurrent statistically significant elevated measures of association in males (OR 1.2-1.4) depending on the degree of exposure to benzene (Pesch 2000). Measures of association were more varied in females (OR 0.9-1.4).

Occupational Exposures, Canada

A Canadian national cancer registry-based case control study identified a statistically significantly elevated measure of association (aOR 1.8) and a monotonic exposure-response for duration of exposure with greater than 6 years demonstrating an elevated measure of association (aOR 2.1) in males (Hu 2002). An elevated measure of association (aOR 1.3) was also seen in females.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Oil Refinery Workers, Finland

A nested case-referent study within a larger cohort study of Finnish oil refinery workers demonstrated an elevated measure of association (OR 2.11) with kidney cancer diagnosis (Anttila 2015). Monotonic exposure-responses were identified for duration of exposure: <1 to 9 yrs=OR 1.37, 10-19 yrs=OR 2.37, and at least 20 yrs=OR 2.98 as well as cumulative exposure: 0.001-0.19mg/m^3*yr=OR 1.69 and 0.20-2.40mg/m^3*yr=OR 2.56. Non-monotonic exposure-response relationships were also presented for cumulative exposure in logistic regression: 0.001–0.19mg/m^3*yr=OR 4.51 and 0.20-2.40mg/m^3=OR 0.96 and for mean annual exposure: 0.0015-0.050mg/m^3=OR 2.69 and 0.0055-0.15 mg/m^3=OR 1.56.

Meta-analysis

Investigators examined 31 studies of benzene exposures with kidney cancer combined with unspecified urinary tract cancers as an outcome. Many of the included studies did not explicitly assess benzene exposure, using occupation as a proxy with frequent co-exposures to other toxins. A statistically significant elevated measure of association (mRR 1.20) was identified in the overall analysis. (Seyyedsalehi 2024).

Bradford Hill: Benzene

An association between benzene exposure and kidney cancer has been identified in multiple studies including occupational exposures and Camp Lejeune water system exposures. The following discussion evaluates the evidence in order to determine whether it is “as likely as not” that this demonstrated association is causal.

Strength of Association: Multiple studies demonstrate elevated measures of association between exposure to benzene and kidney cancer (Anttila 2015; Bove 2014a; Bove 2014b; Gerin 1998; Greenland 1994; Hu 2002; Lynge 1997). These range up to an OR of 4.29 (Greenland 1994). A meta-analysis identified a mRR of 1.20 (Seyyedsalehi 2024). Such a body of literature provides strong evidence that exposure to benzene is a cause of kidney cancer given the demonstrated **strength of association** in the epidemiologic literature.

Consistency: Individual studies of both inhalational occupational exposures (Anttila 2015; Gerin 1998; Greenland 1994; Hu 2002; Lynge 1997) and water system contamination, examining a variety of routes of exposure (Bove 2014a; Bove 2014b) in multiple countries throughout the world provide consistent findings of an association in distinct populations between benzene exposure and kidney cancer. Additionally, analysis of both cancer diagnosis (Anttila 2015; Gerin 1998; Hu 2002; Lynge 1997) and cancer mortality (Bove 2014a; Bove 2014b; Greenland 1994) as the outcome demonstrate similar results. Furthermore, both cohort (Bove 2014a; Bove 2014b; Lynge 1997) and case-control (Anttila 2015; Gerin 1998; Greenland 1994; Hu 2002) studies reach nearly identical conclusions. Such a variety of

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

studies by a multitude of investigators all reaching similar results provide **consistent** evidence that exposure to benzene is a cause of kidney cancer.

Exposure-Response: Monotonic exposure-response relationships have been demonstrated for increased intensity of benzene exposure with increased kidney cancer (Anttila 2015; Gerin 1998; Hu 2002). Additional evidence of exposure-response occurs with other measures of intensity of exposure (Anttila 2015; Bove 2014a; Bove 2014b; Greenland 1994). Similar results despite varied methods of assessing exposure provide compelling evidence of causation given the **exposure-response** relationship demonstrated in multiple studies.

Temporality: Multiple studies utilized prolonged lags to ensure that exposure to benzene occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome of interest (Bove 2014a; Bove 2014b; Greenland 1994). Another study reported "a reasonable period of latency" (Gerin 1998). Such study designs provide evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

Biological Plausibility: Benzene is recognized as a cause of cancer, well established as a cause of leukemia. It is thought that toxic metabolites of benzene are responsible for cancer causation, with t,t-muconic acid and p-benzoquinone as the most likely causative metabolites (Ahmed Kahn 2007). In vitro studies demonstrate DNA damage after exposure to these metabolites. Research is lacking to elucidate the full pathway for exposure to benzene and development of kidney cancer. However, given that benzene is a known human carcinogen and that "benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies," it is scientifically reasonable to conclude that there is a **biologically plausible** mechanistic pathway for benzene to cause kidney cancer.

Analogy: Currently, there is a lack of **analogous** evidence to support benzene as a cause of kidney cancer.

Experiment: There is no human **experimental** evidence of causation involving benzene and kidney cancer. An absence of experimental data is common when considering the body of evidence surrounding occupational or environmental toxins. Of note, a lack of relevant experimental studies does not provide evidence against causation.

Specificity: Benzene exposure has been identified with higher measures of association for kidney cancer in men rather than women (Hu 2002; Lynge 1997). However, it is not clear if this is due to differences in exposure assessment or true differences in susceptibility to kidney cancer by sex. There are multiple possible causes of kidney cancer and multiple types of kidney cancer that were contained in each analysis of benzene exposure and kidney cancer limiting **specificity** in contributing to causation.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Coherence: The human literature provides a coherent body of evidence for benzene exposure as a cause of kidney cancer, albeit less robust compared to TCE and PCE. There is limited supportive animal or mechanistic data in the current literature. However, there is no substantial contrary data suggesting an alternative explanation for the observed measures of association.

Summary: Benzene

The evidence surrounding benzene exposures and the outcome of kidney cancer discussed above is substantial. Given the weight of evidence presented in the Bradford Hill analysis, the "as likely as" standard is satisfied.

Additionally, the 2017 ATSDR framework is also clearly met:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

A meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, i.e., ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence."

In this case, a meta-analysis demonstrates a risk estimate with an elevated measure of association. The weight of evidence indicates that benzene is at least "as likely as not" a cause of kidney cancer.

<u>Exposure: Vinyl Chloride</u>

Cohort Studies

Vinyl Chloride Production Workers, United States

No elevated measure of association (SMR 1.08) with kidney cancer was seen in the cohort of vinyl chloride exposed chemical workers (Mundt 2000). However, an elevated measure of association (SMR 1.16) was identified with additional follow up (Mundt 2017).

Camp Lejeune

An elevated measure of association (HR 1.55) for kidney cancer deaths was identified in a 10-year lagged analysis of military personnel stationed at Camp Lejeune compared to Camp Pendleton with at least low exposure to vinyl chloride (Bove 2014a). Elevated measures of association were identified for all levels of exposure although the exposure response relationship was nonmonotonic. In a similar analysis of

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

civilian personnel, all kidney cancer deaths were exposed to greater than the median vinyl chloride exposure, although the numbers were too small to calculate a measure of association (Bove 2014b).

Case-Control Studies

National Cancer Registry, Canada

A Canadian national cancer registry-based case control study identified a statistically significantly elevated measure of association (aOR 2.0) and monotonic dose response with an aOR for highest duration of exposure (>20 years) of 4.5 in males (Hu 2002). An elevated measure of association (aOR 1.6) was also seen in females.

Bradford Hill: Vinyl Chloride

An association between vinyl chloride exposure and kidney cancer has been identified in two studies including occupational exposures and Camp Lejeune water system exposures. The following discussion evaluates the evidence in order to determine whether it is "as likely as not" that this demonstrated association is causal.

Strength of Association: Multiple studies demonstrate elevated measures of association between exposure to vinyl chloride and kidney cancer (Bove 2014a; Hu 2002; Mundt 2017). These include a HR of 1.55 in an analysis of the entire cohort at Camp Lejeune (Bove 2014a). Even higher measures of association in males (aOR 2.0) and females (aOR 1.6) were seen in an analysis segregated by sex (Hu 2002). Such a body of literature provides sufficient evidence that exposure to vinyl chloride is a cause of kidney cancer given the demonstrated **strength of association** in the epidemiologic literature.

Consistency: Two studies of largely inhalational occupational exposures (Hu 2002; Mundt 2017) and two of water system contamination were conducted, examining a variety of routes of exposure (Bove 2014a; Bove 2014b) in multiple countries provide consistent findings of an association in distinct populations between vinyl chloride exposure and kidney cancer. Additionally, analysis of both cancer diagnosis (Hu 2002) and cancer mortality (Bove 2014a; Bove 2014b; Mundt 2017) as the outcome demonstrate similar results. Furthermore, both cohort (Bove 2014a; Bove 2014b; Mundt 2017) and case-control (Hu 2002) studies reach nearly identical conclusions. The variety of studies by a separate investigators all reaching similar results provide limited but **consistent** evidence that exposure to vinyl chloride is a cause of kidney cancer.

Exposure-Response: Monotonic exposure-response relationships have been demonstrated for increased intensity of vinyl chloride exposure with increased kidney cancer (Hu 2002). Additional evidence of exposure-response occurs with other measures of intensity of exposure (Bove 2014a). Similar results despite varied methods of assessing exposure provide limited but compelling evidence of causation given the **exposure-response** relationship demonstrated in multiple studies.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Temporality: Two studies utilized prolonged lags to ensure that exposure to vinyl chloride occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome of interest (Bove 2014a; Bove 2014b). Such a study design provides evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

Biological Plausibility: Vinyl chloride is recognized as a cause of cancer, well established as a cause of angiosarcomas of the liver and hepatocellular carcinoma. Further, an increased rate of DNA adduct formation in the kidneys have been found. Additionally, both the parent compound of vinyl chloride as well as its metabolites are renally excreted. Vinyl chloride is thought to assert oncogenic ability on the *RAS* and P53 genes. Research is lacking to elucidate the full pathway for exposure to vinyl chloride and development of kidney cancer. However, IARC has stated that, "there is sufficient evidence in humans for the carcinogenicity of vinyl chloride…There is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride." It is scientifically reasonable to conclude that there is a **biologically plausible** mechanistic pathway for vinyl chloride to cause kidney cancer.

Analogy: Currently, there is a lack of **analogous** evidence to support vinyl chloride as a cause of kidney cancer.

Experiment: There is no human **experimental** evidence of causation involving vinyl chloride and kidney cancer. An absence of experimental data is common when considering the body of evidence surrounding occupational or environmental toxins. Of note, a lack of relevant experimental studies does not provide evidence against causation.

Specificity: Vinyl chloride exposure has been identified with higher measures of association for kidney cancer in women rather than men (Hu 2002). However, it is not clear if this is due to differences in exposure assessment or true differences in susceptibility to kidney cancer by sex. There are multiple possible causes of kidney cancer and multiple types of kidney cancer that were contained in each analysis of vinyl chloride exposure and kidney cancer limiting **specificity** in contributing to causation.

Coherence: The human literature provides a limited but **coherent** body of evidence for vinyl chloride exposure as a cause of kidney cancer. There is limited supportive animal or mechanistic data. There is no substantial contrary data suggesting an alternative explanation for the observed measures of association.

Summary: Vinyl Chloride

The evidence surrounding vinyl chloride exposures and the outcome of kidney cancer discussed above is limited but sufficient to establish causation. Given the weight of evidence presented in the Bradford Hill analysis, the "as likely as not" standard is satisfied.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Additionally, the 2017 ATSDR framework is also clearly met:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence."

In this case, two high utility epidemiological studies have been performed and demonstrate consistent risk estimates with elevated measures of association, meeting or exceeding the criteria set forth by ATSDR. Exposure to vinyl chloride is at least as likely as not a cause of kidney cancer.

Levels of Toxic Exposures that are Hazardous to Humans Generally and are Known to Cause Kidney Cancer

Determination of the levels of exposure that are hazardous to humans, and known to cause kidney cancer, follows a framework of evidence. The most relevant literature provides estimates aligned with the population and exposure of concern. Accordingly, if these publications are sufficient to inform the question of exposure levels associated with the outcome of interest, there is no need to turn to alternative exposure metrics from the greater body of literature. Of note, unless specific subgroup analyses of vulnerable populations occur, then reported levels of exposures are likely to be overestimated for such individuals. This means that the lowest levels of reported associations in the scientific literature likely and probably do not represent actual minimum threshold doses. It is unlikely that a true minimum exposure will ever be studied given ethics and safety concerns. However, with reasonable scientific certainty and based on sound scientific principles and methodology, we can detail levels of exposure to the toxins at issue that are hazardous to humans and are known to cause kidney cancer.

There is an order of examination that is most appropriate in identifying low ranges of exposure associated with hazards to human health and that are known to cause kidney cancer. Given that the exposure of interest is water contaminated with multiple culprit compounds, the body of literature that directly examines the Camp Lejeune population exposed to the contaminated water system as measured by either duration of residence or the sum of culprit compounds (TVOC) provides the most direct evidence for exposures at Camp Lejeune. Although the exposed group in this cohort is limited to those on base 1972-1985, Camp Lejeune exposures outside of this time window are similar in composition, although different in intensity, to the analyzed period with the primary exception of minimal PCE exposure prior to this period in the Hadnot Point water system (ATSDR PHA 2017).

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

It is not likely that the majority of exposed were limited to a single water system on the base. However, TCE exposures dwarfed PCE exposures in the Hadnot Point water system, rendering such a difference in exposure composition largely irrelevant when using TVOC or duration as exposure metrics. Consequently, exposure levels associated with an increased risk of kidney cancer directly from the population of interest, with the exposure of interest, represent the best estimates of lower exposure levels hazardous to humans generally and known to cause kidney cancer.

When a monotonic dose response is identified in this population, the lowest exposure metric with an elevated measure of association provides a conservative assessment of a lower exposure level hazardous to humans generally and known to cause kidney cancer. The true bound for equipoise is somewhere below this point, so the reported range is a conservative assessment of an exposure hazardous to human health taken directly from real world exposures. The presence of a monotonic dose response may allow for extrapolation to exposures outside of the studied population, providing an opportunity to extrapolate to exposures lower than the lowest exposure metric that exists.

Given that the exposure of interest is water contaminated with multiple culprit compounds, the body of literature that directly examines the Camp Lejeune population exposed to the contaminated water system best answers the question of what levels of exposure are associated with kidney cancer.

The most relevant evidence for on-base exposures is a monotonic exposure-response relationship with TVOC rather than any individual component exposure (Bove 2014a). Thus, the lowest exposure category to cumulative TVOC with a monotonic dose-response provides evidence of a low level of Camp Lejeune water that is hazardous to human health and a known cause of kidney cancer. This is the “low” exposure group of >1 to 4600 ug/L*month (HR 1.42) in the Bove 2014a study.

Alternatively, a duration-based intensity of exposure is also supported by the Camp Lejeune literature with a monotonic exposure response evident (Bove 2024b). Consequently, the lowest duration category in the monotonic exposure-response finding that demonstrates an elevated measure of association is a level that is hazardous to human health and a known cause of kidney cancer. This is the “low” duration group with 1-5 quarters on base (HR 1.36).

To summarize, if an individual was present at Camp Lejeune and exposed to the levels of the chemicals above, this individual would have been exposed to levels of the water at Camp Lejeune that are hazardous to humans generally and are known to cause kidney cancer.

There are additional ways to identify low levels of the chemicals at issue that are hazardous to humans generally and that are known to cause kidney cancer. One such method is to determine the lowest exposure metric with an elevated measure of association, even if there is not a monotonic response, in the Camp Lejeune population for the outcome of interest. The true bound for equipoise is still

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

somewhere below this point, so this forms a conservative assessment taken directly from real world exposures.

A duration-based intensity of exposure method is supported by the Camp Lejeune literature with a non-monotonic exposure response evident in two studies (Bove 2024a; Bove 2024b). Consequently, the lowest duration category in the nonmonotonic exposure-response finding is a level that demonstrates an elevated measure of association. In these studies, this is the “low” duration group stationed on base in studies using an outcome of kidney cancer diagnosis (HR 1.12) for a duration of 1 to 6 quarters (Bove 2024a) and using an outcome of kidney cancer mortality (HR 1.33) for a duration of 1 to 2 quarters (Bove 2024b) on base.

An additional method of determining low levels of exposure sufficient to cause kidney cancer is to examine a contaminant with a monotonic exposure response and a strong connection to the outcome of interest in the non-Camp Lejeune body of literature. Of note, limitation of exposure to a single compound in isolation necessarily overestimates even the lowest levels of exposure given that the impact of combined exposures is ignored. Again, these low exposure levels with an elevated measure of association are demonstrably hazardous to humans generally and known to cause kidney cancer. However, the true bound for equipoise is somewhere below this point, so reported exposures form a conservative assessment of level hazardous to human health taken directly from the real world. The presence of a monotonic dose response may allow for extrapolation to exposures outside of the studied population, providing an opportunity to extrapolate to exposures lower than the lowest exposure metric that exists.

TCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A monotonic exposure-response relationship with TCE is evident (ATSDR 2018). Consequently, this low exposure to TCE that is demonstrably hazardous to humans at Camp Lejeune is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the “medium” exposure group (OR 1.33 compared to Camp Pendleton; OR 1.45 in internal analysis of Camp Lejeune personnel only) of 110 to <11030 ug/L*month.

PCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A monotonic exposure-response relationship with PCE is evident (ATSDR 2018). Consequently, a low exposure to PCE that is demonstrably hazardous to humans at Camp Lejeune is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the “medium” exposure group (OR 1.28 compared to Camp Pendleton; OR 1.43 in internal analysis of Camp Lejeune personnel only) of 36 to <711 ug/L*month.

If a monotonic dose response is not identified, then the lowest exposure category with an elevated measure of association for an individual contaminant exposure in the Camp Lejeune population for the outcome of interest represents the best estimate of an exposure where equipoise is exceeded to be

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

hazardous to humans and known to cause kidney cancer. However, the true bound for equipoise is somewhere below this point, so this forms a conservative assessment of a low exposure taken directly from real world exposures.

TCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A non-monotonic exposure-response relationship with TCE is evident (Bove 2014a). Consequently, a low exposure to TCE that is demonstrably hazardous to humans at Camp Lejeune is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "low" exposure group (HR 1.54) of >1 to 3100 ug/L*month.

PCE is a single Camp Lejeune water contaminant with sufficient body of evidence for causation of kidney cancer. A non-monotonic exposure-response relationship with PCE is evident (Bove 2014a). Consequently, a low exposure to PCE that is demonstrably hazardous to humans at Camp Lejeune is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "low" exposure group (HR 1.40) of >1 to 155 ug/L*month.

Benzene is a single Camp Lejeune water contaminant with a body of evidence that meets the as likely as not standard for causation of kidney cancer. A non-monotonic exposure-response relationship with benzene is evident (Bove 2014a). Consequently, an exposure to benzene that is demonstrably hazardous to humans at Camp Lejeune and is causally associated with kidney cancer is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "low" exposure group (HR 1.31) of 2 to 45 ug/L*month. Additionally, exposure to benzene was measured in another Camp Lejeune study (Bove 2014b). Median exposures were 4.1 ug/L*month. Exposures of at least the median were associated with kidney cancer (HR 1.82).

Vinyl chloride is a single Camp Lejeune water contaminant with a body of evidence that meets the as likely as not standard for causation of kidney cancer. A non-monotonic exposure-response relationship with vinyl chloride is evident (Bove 2014a). Consequently, an exposure level to vinyl chloride that is demonstrably hazardous to humans at Camp Lejeune and causally related to kidney cancer is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "low" exposure group (HR 1.66) of >1 to 205 ug/L*month.

Another scientifically valid method of determining low levels of toxins that are hazardous to humans and a cause of kidney cancer is to turn to the non-Camp Lejeune literature. In that instance, a contaminant with a monotonic exposure response and a strong connection to the outcome of interest in the non-Camp Lejeune body of literature should be considered first. Of note, consideration of exposures as a single compound in isolation ignores the impact of combined exposures. Additionally, much of the literature on individual compounds consists of occupational exposures, mostly inhalational, which differ from combined residential and occupational exposures that occurred at Camp Lejeune. These two factors likely serve to overestimate the lower range of the magnitude of exposures that are hazardous

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

to human health. When a monotonic dose response is identified for this exposure, then the lowest exposure metric with an elevated measure of association for the outcome of interest represents the best estimate of the point where equipoise is exceeded. However, the true bound for equipoise is somewhere below this point, so this represents a conservative assessment of a low exposure taken directly from real world exposures. The presence of a monotonic dose response may allow for extrapolation to exposures outside of the studied population, potentially estimating the point of equipoise.

TCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A monotonic exposure-response relationship with TCE in a French population-based case-control study is evident (Charbotel 2006). Consequently, a low exposure to TCE that is demonstrably hazardous to humans and causally related to kidney cancer is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "low/medium-no peak" exposure group (aOR 1.35) of 1-150 ppm*years. The cited study formed the basis of the EPA's dose extrapolation for kidney cancer risk.

Benzene is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A monotonic exposure-response relationship with benzene in a Finnish oil refinery worker case-control study is evident utilizing two measures of exposure intensity (Anttila 2015). Consequently, a low exposure to benzene that is demonstrably hazardous to humans and causally related to kidney cancer is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is a cumulative exposure of 0.001-0.19 mg/m^3*year (OR 1.69).

If a monotonic dose response is not identified, then the lowest exposure metric with an elevated measure of association for the outcome of interest represents the best estimate of levels hazardous to human health that and are a known cause of kidney cancer. However, the true bound for equipoise is somewhere below this point, so this represents a conservative assessment of a minimum exposure taken directly from real world exposures. This is yet another scientifically valid method for determining low levels of exposure that meet the standards in this case.

TCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A non-monotonic exposure-response relationship with TCE in a contaminated water supply in New Hampshire is evident (Andrew 2022). This exposure is similar in quality to the Camp Lejeune water system although limited to TCE. Consequently, a low exposure to TCE that is demonstrably hazardous to humans is the lowest cumulative exposure category that demonstrates an elevated measure of association. This is the "50-75th percentile" exposure group (OR 1.78) of >0 to 27.6 ug/L.

PCE is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A non-monotonic exposure-response relationship with PCE in a contaminated water

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

supply in Massachusetts is evident (Aschengrau 1993). Consequently, a low exposure to PCE that is demonstrably hazardous to humans and causally related to kidney cancer is the lowest cumulative exposure category that demonstrates an elevated measure of association. The degree of exposure was not directly quantified in this study, but estimated contamination was 1.5-80 ug/L of PCE in high use sites. The degree of exposure demonstrably hazardous to human health is the lowest exposure category to PCE in the non-monotonic dose-response finding that demonstrates an elevated measure of association with kidney cancer diagnosis. This is the "low" exposure group of up to the 90th percentile (relative delivered dose in controls of 27.1 mg) with an estimated minimum relative delivered dose of >0 mg (OR 1.36). In exposed, the estimated dose delivered ranged from 10-209,400ug (Webler 1993). Direct measurements from the water system demonstrated median (66ug/L), mean (0.5ug/L), and a range (ND to 2432ug/L) of PCE concentrations similar to Camp Lejeune (Spence 2008).

Benzene is a single Camp Lejeune water contaminant with a sufficient body of evidence for causation of kidney cancer. A non-monotonic exposure-response relationship with benzene in a Finnish oil refinery worker case-control study is evident utilizing two measures of exposure intensity (Anttila 2015). Consequently, a low exposure to benzene that is demonstrably hazardous to humans and causally related to kidney cancer is the lowest exposure category that demonstrates an elevated measure of association. This is a cumulative exposure in a logistic regression of 0.001 to 0.19mg/m^3*year (OR 4.51). Analyzed in terms of mean annual exposure, 0.0015 to 0.050mg/m^3 (OR 2.69) provides an additional "low" exposure group that is hazardous to human health and a cause of kidney cancer.

To reiterate, this stepwise approach to the evidence simply indicates the order in which evidence should be evaluated in determining the low levels of exposure that are known to be hazardous to humans generally and are known causes of kidney cancer. This methodology is based on my many years of education, training and experience as detailed above in this report.

Studies detailing the levels that are hazardous to humans and that are known to cause kidney cancer are also abstracted in the attached appendix (see appendix 1: table).

Non-Human Studies

When considering whether animal or mechanistic studies of exposures to TCE, PCE, vinyl chloride, and benzene with kidney cancer as an outcome are contributory, it is important to remember the standard for causation organizing this review:

"Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

1. The degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality" (ATSDR 2017)

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

For Camp Lejeune exposures, there is sufficient evidence in human studies to conclude that water contamination is known to cause kidney cancer. Nevertheless, confirmation of kidney cancer causation following at least one culprit exposure, particularly in exposed mammals, would provide further support for this conclusion. Likewise, elucidation of a plausible pathway for kidney cancer causation for at least one culprit exposure furthers the discussion. However, the absence of either supportive animal evidence or confidence in a biologic pathway would not raise concern with a conclusion based upon sufficient human evidence.

Animal Studies

Multiple rat studies of TCE exposures via varied routes identified excess kidney cancers. The first TCE study where kidney tumors developed in animals was a female rodent study of inhalational TCE exposure (Fukuda 1983). One rat developed a clear cell carcinoma, although the results were not statistically significant. A subsequent inhalational study examined both male and female rats (Maltoni 1988). In male rats exposed via an inhalational route, excess renal tubular cell cancers occurred. Such a type of tumor had never been observed in this rat species. The cortical tumor type seen in females in the same study had been observed infrequently in controls, although excess tumors were identified. Two gavage (ingestion) exposure studies of rats were conducted by the National Toxicology Program (NTP 1988; NTP 1990). The initial study found increased kidney tumors following TCE exposure in four strains of rats (NTP 1988). A subsequent study demonstrated significantly elevated numbers of kidney tumors in male rats of another species where historical controls rarely demonstrate kidney tumors (NTP 1990). Moreover, a similar rat study using the same species found increased kidney tumors in male rats exposed to PCE (NTP 1986). These animal studies demonstrate biologically significant findings, with kidney cancer development in multiple rat species exposed via both inhalational and ingestion exposures to TCE. Such findings provide support for the conclusion that exposure to Camp Lejeune water via both inhalation and ingestion is a cause of kidney cancer.

The evidence of benzene as a cause of kidney cancer in animal studies is limited. One study demonstrated an increased incidence of nephroblastomas (a type of kidney cancer) in rats although the authors did not conclude that this was a causal association (Maltoni 1981).

Mechanistic Studies

A pathway for kidney cancer development following TCE exposure has been elucidated. TCE undergoes both oxidative metabolism in the liver as well as glutathione conjugation in the liver and kidney (EPA 2011; Chiu 2013). Following conjugation, TCE becomes S-dichlorovinyl-L-glutathione (DCVG), is concentrated in the kidney, and then becomes S-dichlorovinyl-L-cysteine (DCVC). Although untransformed TCE is not particularly toxic, DCVG and DCVC both demonstrate mutagenicity (Dekant 1986, Vamvakas 1987, Vamvakas 1988). Moreover, studies with isolated animal (rat, rabbit,

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

and pig) and human renal cells provide evidence of both genotoxicity and mutagenicity in kidney tissue exposed to DCVG and DCVC (Jaffe 1995, Vamvakas 1989, Robbiano 1998, Robbiano 2004). It is suspected that regenerative cell proliferation following cytotoxicity also plays a role in tumorogenesis (Mally 2006). Additionally, oxidative stress is also well-known factor in cancer development.

Of note, metabolic data for PCE is more limited than for TCE, although a glutathione conjugation pathway has been elucidated, resulting in S-(1,2,2-trichlorovinyl)-L-glutathione (TCVG) and S-(1,2,2-trichlorovinyl)-L-cysteine (TCVC) (Lash 1998, IARC 2014, Guyton 2014). TCVG and TCVC both demonstrate mutagenicity (Dekant 1986, Vamvakas 1987, Dreeson 2003). Studies with isolated pig kidney cells show evidence of increased unscheduled DNA synthesis (Vamvakas 1989). Although less well studied, PCE appears to undergo metabolism via glutathione conjugation in a similar fashion to TCE, with some evidence that an even greater proportion of PCE is transformed via this pathway in comparison to TCE (Lash 1998, IARC 2014, Guyton 2014).

Crucially, the carcinogenicity of glutathione metabolites is supported by human epidemiologic research. In a case control study, TCE exposure demonstrated a statistically significant association (OR 1.88) with development of kidney cancer in those with an intact glutathione conjugation system, i.e. an active GSTT1 (glutathione-S-transferase theta-1) enzyme (Moore 2010). However, in those with an inactive glutathione conjugation system, i.e. an inactive GSTT1, no elevated measure of association (OR 0.93) was seen. This provides direct human support for the proposed carcinogenic pathway and further bolsters the determination that Camp Lejeune water exposure meets the equipoise and above standard for causation of kidney cancer. Given that non-parenchymal upper urinary tract (renal pelvis and ureter) shares blood supply from the renal artery with the body of the kidney and that urine flows from the kidney through the renal pelvis and ureter it is at least as likely as not that urothelial cancers share the described carcinogenic mechanism with kidney cancers.

Benzene is recognized as a cause of cancer, well established as a cause of leukemia. It is thought that toxic metabolites of benzene are responsible for cancer causation, with t,t-muconic acid and p-benzoquinone as the most likely causative metabolites (Ahmed Kahn 2007). In vitro studies demonstrate DNA damage after exposure to these metabolites. Currently, the literature base is too limited to define a precise pathway or mechanism of injury for benzene exposure leading to the development of kidney cancer. However, given that benzene is a known human carcinogen and that "benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies," it is reasonable to conclude that there is a plausible pathway for benzene to cause kidney cancer.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Vinyl chloride is recognized as a cause of cancer, well established as a cause of angiosarcomas of the liver and hepatocellular carcinoma. Further, an increased rate of DNA adduct formation in the kidneys have been found. Additionally, both the parent compound of vinyl chloride as well as its metabolites are renally excreted. Vinyl chloride is thought to assert oncogenic ability on the *RAS* and P53 genes. Currently, the literature base is too limited to define a precise pathway or mechanism of injury for vinyl chloride exposure leading to the development of kidney cancer. However, IARC has stated that, "there is sufficient evidence in humans for the carcinogenicity of vinyl chloride…there is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride." It is reasonable to conclude that there is a plausible pathway for vinyl chloride to cause kidney cancer.

VII Scientific Agencies

Various scientific agencies have examined the question of whether Camp Lejeune exposure itself, or component culprit exposures are a cause of kidney cancer in humans. Consistent determinations by multiple scientific panels evaluating the causal question indicate the determination that Camp Lejeune water exposure meets the equipoise and above standard for causation of kidney cancer and is in line with current evaluation of the evidence. Furthermore, such unanimity reflects general consensus in the scientific community on this question.

Camp Lejeune

Multiple reports have focused on Camp Lejeune exposures as the primary exposure. The initial evaluation was conducted by the National Research Council of the National Academies of Science (NRC 2009). The evaluation occurred prior to the publication of Camp Lejeune specific cohort studies published, finding "limited/suggestive evidence" of an association between Camp Lejeune exposures and kidney cancer. Such a connection is equivalent to the "equipoise and above" standard for causation. This was primarily driven by evidence connecting TCE and PCE exposures to kidney cancer. A follow up document by the Institute of Medicine in 2015 stated that "new studies have generally supported the conclusions of the previous report (IOM 2015)." An ATSDR evaluation of the available evidence in 2017 concluded that "there is sufficient evidence for causation for TCE and kidney cancer" but "below equipoise evidence for causation for PCE and kidney cancer (ATSDR 2017)." Additional evidence since these publications has not weakened the assessment of evidence. Rather, the connection between Camp Lejeune exposures and kidney cancer has only strengthened for Camp Lejeune exposures as well as for exposures to each of the individual toxins at issue.

TCE

Culprit exposures have also been analyzed individually and uniformly identified TCE as a cause of kidney cancer. The EPA review of TCE concluded that there is "convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The kidney cancer association cannot be

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

reasonably attributed to chance, bias, or confounding (EPA 2011; EPA IRIS 2011; EPA 2020). It has also determined that "TCE is carcinogenic to workers … by all routes of exposure. This is most strongly supported by the data on kidney cancer" (EPA 2022). The most recent IARC monograph classified TCE as Group 1, carcinogenic to humans (IARC 2014). It states that "There is sufficient evidence in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney." Likewise, the NTP monograph confirms that the body of epidemiologic evidence "demonstrated a causal relationship between trichloroethylene exposure and kidney cancer" (NTP 2015). Furthermore, the ATSDR has also concluded that "there is strong evidence that trichloroethylene can cause kidney cancer in people" (ATSDR 2019). Additional evidence since these publications has not weakened the assessment of evidence. Rather, the connection between TCE exposures and kidney cancer has only strengthened.

Other culprit exposures

Other culprit exposures have less frequent reviews for kidney cancer as an outcome. The most recent IARC monograph classified PCE as Group 2A (probably carcinogenic to humans) finding that "there is limited evidence in humans for the carcinogenicity of PCE" with the strongest evidence for bladder cancer (IARC 2014). Benzene was reviewed by IARC and found to be a Class 1 agent, carcinogenic to humans (IARC 2012, IARC 2018). However, this is based on sufficient evidence in humans to conclude that exposure "causes acute myeloid leukaemia." Likewise, vinyl chloride was also reviewed by IARC and found to be a Class 1 agent, carcinogenic to humans (IARC 2008, IARC 2012). However, this is based on sufficient evidence in humans to conclude that exposure "causes angiosarcomas of the liver and hepatocellular carcinomas." Evidence since the last IARC reviews only provides additional support for exposure to each agent as a cause of kidney cancer. Furthermore, additional agencies have made similar determinations (ATSDR 2024; NTP 2021).

In summary, there is consensus in the scientific community, including by US government agencies, that there is sufficient evidence for a causal association between Camp Lejeune water exposures and kidney cancer.

VIII Conclusions

Based on my education, training, and experience, along with a review of the material cited herein or otherwise identified, I hold the following opinions:

- Exposure to contaminated water at Camp Lejeune is a cause of kidney cancer
- TCE exposure via the contaminated water at Camp Lejeune is a cause of kidney cancer
- PCE exposure via the contaminated water at Camp Lejeune is a cause of kidney cancer
- Benzene exposure via the contaminated water at Camp Lejeune is a cause of kidney cancer

Toxicology Associates, Prof. LLC
Dedicated to Patient Care, Research, and Teaching in Medical Toxicology

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

- Vinyl chloride exposure via the contaminated water at Camp Lejeune is a cause of kidney cancer
- Cumulative TVOC exposure of >1 to 4600 ug/L*month or duration of 1-5 quarters on base at Camp Lejeune is sufficient to represent an exposure level at Camp Lejeune that is hazardous to humans generally and known to cause kidney cancer. There are multiple other methods for determining levels that are hazardous to humans generally and known to cause kidney cancer, as detailed above.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

IX Materials Considered

Adami HO, Berry SC, Breckenridge CB, Smith LL, Swenberg JA, Trichopoulos D, Weiss NS, Pastoor TP. Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. Toxicol Sci. 2011 Aug;122(2):223-34.

Agency for Toxic Substances and Disease Registry. 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. March 2013.

Agency for Toxic Substances and Disease Registry. Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases. January 13, 2017.

Agency for Toxic Substances and Disease Registry. Public Health Assessment for Camp Lejeune Drinking Water US Marine Corps Base Camp Lejeune, North Carolina. January 20, 2017.

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

Agency for Toxic Substances and Disease Registry. Toxicological Profile for Trichloroethylene. June 2019.

Agency for Toxic Substances and Disease Registry. Toxicological Profile for Vinyl Chloride. January 2024.

Ahmad Khan H. Benzene's toxicity: a consolidated short review of human and animal studies. Hum Exp Toxicol. 2007 Sep;26(9):677-85.

Alanee S, Clemons J, Zahnd W, Sadowski D, Dynda D. Trichloroethylene Is Associated with Kidney Cancer Mortality: A Population-based Analysis. Anticancer Res. 2015 Jul;35(7):4009-13.

Andrew AS, Li M, Shi X, Rees JR, Craver KM, Petali JM. Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. Int J Environ Res Public Health. 2022 Jan 6;19(2):618.

Anttila A, Pukkala E, Sallmén M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995 Jul;37(7):797-806.

Anttila A, Pokhrel A, Heikkilä P, Viinanen R, Pukkala E. Kidney cancer risk in oil refining in Finland: a nested case-referent study. J Occup Environ Med. 2015 Jan;57(1):68-72.

Aschengrau A, Ozonoff D, Paulu C, Coogan P, Vezina R, Heeren T, Zhang Y. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health. 1993 Sep-Oct;48(5):284-92.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Axelson O, Seldén A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med. 1994 May;36(5):556-62.

Blair A, Decoufle P, Grauman D. Causes of death among laundry and dry-cleaning workers. Am J Public Health. 1979 May;69(5):508-11.

Blair A, Haas T, Prosser R, Morrissette M, Blackman K, Grauman D, van Dusen P, Moran F. Mortality among United States Coast Guard marine inspectors. Arch Environ Health. 1989 May-Jun;44(3):150-6.

Blair A, Stewart PA, Tolbert PE, Grauman D, Moran FX, Vaught J, Rayner J. Cancer and other causes of death among a cohort of dry cleaners. Br J Ind Med. 1990 Mar;47(3):162-8.

Blair A, Hartge P, Stewart PA, McAdams M, Lubin J. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Med. 1998 Mar;55(3):161-71.

Blair A, Petralia SA, Stewart PA. Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol. 2003 Jan;13(1):50-6.

Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. Mortality among aircraft manufacturing workers. Occup Environ Med. 1999 Sep;56(9):581-97.

Boice JD Jr, Marano DE, Cohen SS, Mumma MT, Blot WJ, Brill AB, Fryzek JP, Henderson BE, McLaughlin JK. Mortality among Rocketdyne workers who tested rocket engines, 1948-1999. J Occup Environ Med. 2006 Oct;48(10):1070-92.

Bond GG, McLaren EA, Baldwin CL, Cook RR. An update of mortality among chemical workers exposed to benzene. Br J Ind Med. 1986 Oct;43(10):685-91.

Bove FJ. Deposition. October 17-18 2024.

Bove FJ. Evaluation of cancer incidence among Marines and Navy personnel and civilian workers exposed to contaminated drinking water at USMC Base Camp Lejeune: a cohort study. medRxiv preprint. January 29, 2024.

Bove FJ, Greek A, Gatiba R, Boehm RC, Mohnsen MM. Evaluation of mortality among Marines, Navy personnel, and civilian workers exposed to contaminated drinking water at USMC base Camp Lejeune: a cohort study. Environ Health. 2024 Jul 3;23(1):61.

Bove FJ, Ruckart PZ, Maslia M, Larson TC. Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Feb 19;13(1):10.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Bove FJ, Ruckart PZ, Maslia M, Larson TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. Environ Health. 2014 Aug 13;13:68.

Brautbar N, Wu MP, Gabel E, Regev L. Occupational kidney cancer: exposure to industrial solvents. Ann N Y Acad Sci. 2006 Sep;1076:753-64.

Brüning T, Pesch B, Wiesenhütter B, Rabstein S, Lammert M, Baumüller A, Bolt HM. Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. Am J Ind Med. 2003 Mar;43(3):274-85.

Buhagen M, Grønskag A, Ragde SF, Hilt B. Association Between Kidney Cancer and Occupational Exposure to Trichloroethylene. J Occup Environ Med. 2016 Sep;58(9):957-9.

Bulbulyan MA, Ilychova SA, Zahm SH, Astashevsky SV, Zaridze DG. Cancer mortality among women in the Russian printing industry. Am J Ind Med. 1999 Jul;36(1):166-71.

Callahan CL, Stewart PA, Blair A, Purdue MP. Extended Mortality Follow-up of a Cohort of Dry Cleaners. Epidemiology. 2019 Mar;30(2):285-290.

Calvert GM, Ruder AM, Petersen MR. Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. 2011 Oct;68(10):709-16.

Chang YM, Tai CF, Yang SC, Chen CJ, Shih TS, Lin RS, Liou SH. A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan. Ann Epidemiol. 2003 Oct;13(9):652-60.

Chang YM, Tai CF, Yang SC, Lin RS, Sung FC, Shih TS, Liou SH. Cancer incidence among workers potentially exposed to chlorinated solvents in an electronics factory. J Occup Health. 2005 Mar;47(2):171-80.

Charbotel B, Fevotte J, Hours M, Martin JL, Bergeret A. Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg. 2006 Nov;50(8):777-87.

Charbotel B, Gad S, Caïola D, Béroud C, Fevotte J, Bergeret A, Ferlicot S, Richard S. Trichloroethylene exposure and somatic mutations of the VHL gene in patients with Renal Cell Carcinoma. J Occup Med Toxicol. 2007 Nov 12;2:13.

Christensen KY, Vizcaya D, Richardson H, Lavoué J, Aronson K, Siemiatycki J. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal. J Occup Environ Med. 2013 Feb;55(2):198-208.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Chiu WA, Jinot J, Scott CS, Makris SL, Cooper GS, Dzubow RC, Bale AS, Evans MV, Guyton KZ, Keshava N, Lipscomb JC, Barone S Jr, Fox JF, Gwinn MR, Schaum J, Caldwell JC. Human health effects of trichloroethylene: key findings and scientific issues. Environ Health Perspect. 2013 Mar;121(3):303-11.

Collins JJ, Anteau SE, Swaen GM, Bodner KM, Bodnar CM. Lymphatic and hematopoietic cancers among benzene-exposed workers. J Occup Environ Med. 2015 Feb;57(2):159-63.

Costa G, Merletti F, Segnan N. A mortality cohort study in a north Italian aircraft factory. Br J Ind Med. 1989 Oct;46(10):738-43.

Dekant W, Vamvakas S, Berthold K, Schmidt S, Wild D, Henschler D. Bacterial beta-lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. Chem Biol Interact. 1986 Oct 15;60(1):31-45.

Dosemeci M, Cocco P, Chow WH. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med. 1999 Jul;36(1):54-9.

Dreessen B, Westphal G, Bünger J, Hallier E, Müller M. Mutagenicity of the glutathione and cysteine S-conjugates of the haloalkenes 1,1,2-trichloro-3,3,3-trifluoro-1-propene and trichlorofluoroethene in the Ames test in comparison with the tetrachloroethene-analogues. Mutat Res. 2003 Aug 5;539(1-2):157-66

Duh RW, Asal NR. Mortality among laundry and dry cleaning workers in Oklahoma. Am J Public Health. 1984 Nov;74(11):1278-80.

Environmental Protection Agency. Integrated Risk Information System (IRIS). September 2011.

Environmental Protection Agency. TOXICOLOGICAL REVIEW OF TRICHLOROETHYLENE (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). September 2011.

Environmental Protection Agency. Risk Evaluation for Trichloroethylene. CASRN: 79-01-6. November 2020.

Environmental Protection Agency. Unreasonable Risk Determination for Trichloroethylene. December 2022.

Environmental Protection Agency. October 23, 2023. https://www.epa.gov/newsreleases/biden-harris-administration-proposes-ban-trichloroethylene-protect-public-toxic

Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987 Jul 16;317(3):141-5.

Fukuda K, Takemoto K, Tsuruta H. Inhalation carcinogenicity of trichloroethylene in mice and rats. Ind Health. 1983;21(4):243-54.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Garabrant DH, Held J, Langholz B, Bernstein L. Mortality of aircraft manufacturing workers in southern California. Am J Ind Med. 1988;13(6):683-93.

Gérin M, Siemiatycki J, Désy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. Am J Ind Med. 1998 Aug;34(2):144-56.

Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TJ. A case-control study of cancer mortality at a transformer-assembly facility. Int Arch Occup Environ Health. 1994;66(1):49-54.

Guyton KZ, Hogan KA, Scott CS, Cooper GS, Bale AS, Kopylev L, Barone S, Makris SL, Glenn B, Subramaniam RP, Gwinn MR, Dzubow RC, Chiu WA. Human health effects of tetrachloroethylene: key findings and scientific issues. Environ Health Perspect. 2014 Apr;122(4):325-34.

Guzelian PS, Victoroff MS, Halmes NC, James RC, Guzelian CP. Evidence-based toxicology: a comprehensive framework for causation. Hum Exp Toxicol. 2005 Apr;24(4):161-201.

Hansen J, Raaschou-Nielsen O, Christensen JM, Johansen I, McLaughlin JK, Lipworth L, Blot WJ, Olsen JH. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med. 2001 Feb;43(2):133-9.

Hansen J, Sallmén M, Seldén AI, Anttila A, Pukkala E, Andersson K, Bryngelsson IL, Raaschou-Nielsen O, Olsen JH, McLaughlin JK. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. J Natl Cancer Inst. 2013 Jun 19;105(12):869-77.

Harrington JM, Whitby H, Gray CN, Reid FJ, Aw TC, Waterhouse JA. Renal disease and occupational exposure to organic solvents: a case referent approach. Br J Ind Med. 1989 Sep;46(9):643-50.

Henschler D, Vamvakas S, Lammert M, Dekant W, Kraus B, Thomas B, Ulm K. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Arch Toxicol. 1995;69(5):291-9.

Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965 May;58(5):295-300.

Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med (Lond). 2002 May;52(3):157-64.

Institute of Medicine. Improving the Presumptive Disability Decision-Making Process for Veterans. Washington, DC: The National Academies Press. 2008.

Institute of Medicine. Review of VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation. Washington, DC: The National Academies Press. 2015.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

International Agency for Research on Cancer. World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. VOLUME 97. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). 2008.

International Agency for Research on Cancer. World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100 F. Chemical agents and related occupations. 2012.

International Agency for Research on Cancer. World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. VOLUME 106. TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS. 2014.

International Agency for Research on Cancer; World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 120. Benzene. 2018.

Jaffe DR, Hassall CD, Gandolfi AJ, Brendel K. Production of DNA single strand breaks in rabbit renal tissue after exposure to 1,2-dichlorovinylcysteine. Toxicology. 1985 Apr;35(1):25-33.

Jones RR, Purdue MP. Invited Perspective: Insights into Exposure to Industrial Solvents and Cancer Risk at Camp Lejeune. Environ Health Perspect. 2024 Oct;132(10):101304.

Karami S, Lan Q, Rothman N, Stewart PA, Lee KM, Vermeulen R, Moore LE. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Occup Environ Med. 2012 Dec;69(12):858-67.

Katz RM, Jowett D. Female laundry and dry cleaning workers in Wisconsin: a mortality analysis. Am J Public Health. 1981 Mar;71(3):305-7.

Kelsh MA, Alexander DD, Mink PJ, Mandel JH. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology. 2010 Jan;21(1):95-102.

Lash LH, Qian W, Putt DA, Desai K, Elfarra AA, Sicuri AR, Parker JC. Glutathione conjugation of perchloroethylene in rats and mice in vitro: sex-, species-, and tissue-dependent differences. Toxicol Appl Pharmacol. 1998 May;150(1):49-57.

Lipworth L, Sonderman JS, Mumma MT, Tarone RE, Marano DE, Boice JD Jr, McLaughlin JK. Cancer mortality among aircraft manufacturing workers: an extended follow-up. J Occup Environ Med. 2011 Sep;53(9):992-1007.

Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, Boffetta P, Grandjean P, Heikkilä P, Hörte LG, Jakobsson R, Lundberg I, Moen B, Partanen T, Riise T. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol. 1997 Mar 1;145(5):449-58.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Lynge E, Andersen A, Rylander L, Tinnerberg H, Lindbohm ML, Pukkala E, Romundstad P, Jensen P, Clausen LB, Johansen K. Cancer in persons working in dry cleaning in the Nordic countries. Environ Health Perspect. 2006 Feb;114(2):213-9.

Mally A, Walker CL, Everitt JI, Dekant W, Vamvakas S. Analysis of renal cell transformation following exposure to trichloroethene in vivo and its metabolite S-(dichlorovinyl)-L-cysteine in vitro. Toxicology. 2006 Jul 5;224(1-2):108-18.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. Environ Health Perspect. 1981 Oct;41:3-29.

Maltoni C, Lefemine G, Cotti G, Perino G. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. Ann N Y Acad Sci. 1988;534:316-42.

Maslia ML, Suárez-Soto RJ, Wang J, Aral MM, RE Faye, Sautner JB, and Valenzuela C. 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 I: Parameter sensitivity, uncertainty, and variability associated with model simulations of groundwater flow, contaminant fate and transport, and distribution of drinking water. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2008.

Maslia ML, Suárez-Soto RJ, Sautner JB, Anderson BA, Jones LE, Faye RE, Aral MM, Guan J, Jang W, Telci IT, Grayman WM, Bove FJ, Ruckart PZ, and Moore, SM. 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: Summary and Findings. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2013.

Maslia ML. Expert Report. 2024.

McKone TE, Knezovich JP. The transfer of trichloroethylene (TCE) from a shower to indoor air: experimental measurements and their implications. J Air Waste Manage Assoc. 1991 Jun;41(6):832-7.

McLean D, Pearce N, Langseth H, Jäppinen P, Szadkowska-Stanczyk I, Persson B, Wild P, Kishi R, Lynge E, Henneberger P, Sala M, Teschke K, Kauppinen T, Colin D, Kogevinas M, Boffetta P. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry: an international collaborative study. Environ Health Perspect. 2006 Jul;114(7):1007-12.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Moore LE, Boffetta P, Karami S, Brennan P, Stewart PS, Hung R, Zaridze D, Matveev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Gromiec J, Holcatova I, Merino M, Chanock S, Chow WH, Rothman N. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res. 2010 Aug 15;70(16):6527-36.

Morgan RW, Kelsh MA, Zhao K, Heringer S. Mortality of aerospace workers exposed to trichloroethylene. Epidemiology. 1998 Jul;9(4):424-31.

Moro AM, Brucker N, Charão MF, Baierle M, Sauer E, Goethel G, Barth A, Nascimento SN, Gauer B, Durgante J, Amaral BS, Neto FR, Gioda A, Garcia SC. Biomonitoring of gasoline station attendants exposed to benzene: Effect of gender. Mutat Res Genet Toxicol Environ Mutagen. 2017 Jan;813:1-9.

Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942-72: update of cancer mortality to 31 December 1995. Occup Environ Med. 2000 Nov;57(11):774-81.

Mundt KA, Dell LD, Crawford L, Gallagher AE. Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013. Occup Environ Med. 2017 Oct;74(10):709-716.

National Research Council; Committee on Contaminated Drinking Water at Camp Lejeune. Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects. 2009.

National Toxicology Program. Report on Carcinogens 05, Monograph on Trichloroethylene. January 2015.

National Toxicology Program. Report on Carcinogens 15, Monograph on Tetrachloroethylene. 2021.

National Toxicology Program. TOXICOLOGY AND CARCINOGENESIS STUDIES OF TETRACHLOROETHYLENE (PERCHLOROETHYLENE) (CAS NO. 127-18-4) IN F344/N RATS AND B6C3Fi MICE (INHALATION STUDIES). 1986.

National Toxicology Program. TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRICHLOROETHYLENE (CAS NO. 79-01-6) IN FOUR STRAINS OF RATS (ACI, AUGUST, MARSHALL, OSBORNE-MENDEL) (GAVAGE STUDIES). 1988.

National Toxicology Program.CARCINOGENESIS STUDIES OF TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN) (CAS NO. 79-01-6) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES). 1990.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter Urothelial and Renal Cancer. Int J Epidemiol. 2000 Apr;29(2):238-47.

Press DJ, McKinley M, Deapen D, Clarke CA, Gomez SL. Residential cancer cluster investigation nearby a Superfund Study Area with trichloroethylene contamination. Cancer Causes Control. 2016 May;27(5):607-13.

Purdue MP, Stewart PA, Friesen MC, Colt JS, Locke SJ, Hein MJ, Waters MA, Graubard BI, Davis F, Ruterbusch J, Schwartz K, Chow WH, Rothman N, Hofmann JN. Occupational exposure to chlorinated solvents and kidney cancer: a case-control study. Occup Environ Med. 2017 Mar;74(4):268-274.

Purdue MP, Rhee J, Moore L, Gao X, Sun X, Kirk E, Bencko V, Janout V, Mates D, Zaridze D, Petruzella S, Hakimi AA, Linehan WM, Chanock SJ, Brennan P, Furberg H, Troester M, Rothman N. Differences in risk factors for molecular subtypes of clear cell renal cell carcinoma. Int J Cancer. 2021 Oct 1;149(7):1448-1454.

Raaschou-Nielsen O, Hansen J, McLaughlin JK, Kolstad H, Christensen JM, Tarone RE, Olsen JH. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol. 2003 Dec 15;158(12):1182-92.

Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. J Occup Environ Med. 2008 Nov;50(11):1306-19.

Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Environ Med. 1999 Jul;41(7):556-66.

Robbiano L, Mereto E, Migliazzi Morando A, Pastore P, Brambilla G. Increased frequency of micronucleated kidney cells in rats exposed to halogenated anaesthetics. Mutat Res. 1998 Feb 23;413(1):1-6.

Robbiano L, Baroni D, Carrozzino R, Mereto E, Brambilla G. DNA damage and micronuclei induced in rat and human kidney cells by six chemicals carcinogenic to the rat kidney. Toxicology. 2004 Nov 15;204(2-3):187-95.

Ruder AM, Ward EM, Brown DP. Mortality in dry-cleaning workers: an update. Am J Ind Med. 2001 Feb;39(2):121-32.

Scott CS, Jinot J. Trichloroethylene and cancer: systematic and quantitative review of epidemiologic evidence for identifying hazards. Int J Environ Res Public Health. 2011 Nov;8(11):4238-72.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Seyyedsalehi MS, Bonetti M, Shah D, DeStefano V, Boffetta P. Occupational benzene exposure and risk of kidney and bladder cancers: a systematic review and meta-analysis. Eur J Cancer Prev. 2024 Aug 20.

Silver SR, Pinkerton LE, Fleming DA, Jones JH, Allee S, Luo L, Bertke SJ. Retrospective cohort study of a microelectronics and business machine facility. Am J Ind Med. 2014 Apr;57(4):412-24.

Slikker W Jr, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, David RM, Doerrer NG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Setzer RW, Swenberg JA, Wallace K. Dose-dependent transitions in mechanisms of toxicity. Toxicol Appl Pharmacol. 2004 Dec 15;201(3):203-25.

Sorahan T, Kinlen LJ, Doll R. Cancer risks in a historical UK cohort of benzene exposed workers. Occup Environ Med. 2005 Apr;62(4):231-6.

Spinelli JJ, Demers PA, Le ND, Friesen MD, Lorenzi MF, Fang R, Gallagher RP. Cancer risk in aluminum reduction plant workers (Canada). Cancer Causes Control. 2006 Sep;17(7):939-48.

Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med. 1991 Aug;48(8):515-30.

Sung TI, Chen PC, Jyuhn-Hsiarn Lee L, Lin YP, Hsieh GY, Wang JD. Increased standardized incidence ratio of breast cancer in female electronics workers. BMC Public Health. 2007 Jun 8;7:102.

Vamvakas S, Dekant W, Berthold K, Schmidt S, Wild D, Henschler D. Enzymatic transformation of mercapturic acids derived from halogenated alkenes to reactive and mutagenic intermediates. Biochem Pharmacol. 1987 Sep 1;36(17):2741-8.

Vamvakas S, Elfarra AA, Dekant W, Henschler D, Anders MW. Mutagenicity of amino acid and glutathione S-conjugates in the Ames test. Mutat Res. 1988 Sep;206(1):83-90.

Vamvakas S, Dekant W, Henschler D. Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine S-conjugates of haloalkenes and haloalkanes. Mutat Res. 1989 Apr;222(4):329-35.

Vamvakas S, Brüning T, Thomasson B, Lammert M, Baumüller A, Bolt HM, Dekant W, Birner G, Henschler D, Ulm K. Renal cell cancer correlated with occupational exposure to trichloroethene. J Cancer Res Clin Oncol. 1998;124(7):374-82.

Vandenberg LN, Rayasam SDG, Axelrad DA, Bennett DH, Brown P, Carignan CC, Chartres N, Diamond ML, Joglekar R, Shamasunder B, Shrader-Frechette K, Subra WA, Zarker K, Woodruff TJ. Addressing systemic problems with exposure assessments to protect the public's health. Environ Health. 2023 Jan 12;21(Suppl 1):121.

Jeffrey Brent, MD, PhD
Ken Kulig, MD
Edward W. Cetaruk, MD
Nicklaus Brandehoff, MD

26 West Dry Creek Circle, Suite 815
Littleton, CO, 80120
Phone: 720-477-2500
Fax: 720-598-0409

Robert B. Palmer, PhD
Benjamin Hatten, MD, MPH
William J. Boroughf, DO
Alexa Camarena-Michel, MD

Varshavsky JR, Rayasam SDG, Sass JB, Axelrad DA, Cranor CF, Hattis D, Hauser R, Koman PD, Marquez EC, Morello-Frosch R, Oksas C, Patton S, Robinson JF, Sathyanarayana S, Shepard PM, Woodruff TJ. Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environ Health. 2023 Jan 12;21(Suppl 1):133.

Vlaanderen J, Straif K, Pukkala E, Kauppinen T, Kyyrönen P, Martinsen JI, Kjaerheim K, Tryggvadottir L, Hansen J, Sparén P, Weiderpass E. Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Occup Environ Med. 2013 Jun;70(6):393-401.

Wartenberg D, Reyner D, Scott CS. Trichloroethylene and cancer: epidemiologic evidence. Environ Health Perspect. 2000 May;108 (Suppl 2):161-76.

Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. Br J Ind Med. 1987 Jun;44(6):365-81.

Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. Br J Ind Med. 1987 Jun;44(6):382-95.

Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, Ritz B. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. Am J Ind Med. 2005 Oct;48(4):249-58.

APPENDIX I – KIDNEY CANCER EXPOSURE CHART

Author	Year	Measure of association	Exposure	Dose-Response	Lag/latency	Renal Pelvis	Notes
Camp Lejeune							
Bove (b-civilian)		2014 HR 1.92 (mortality) in employees of Camp Lejeune	Monthly median water system contamination: TCE=356.6ug/L; PCE=14.5ug/L; Vinyl Chloride=20.3ug/L; Benzene=4.1ug/L	Median or greater cumulative TVOC exposure=HR 4.44	10 years (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune civilian employees 1973-1985
ATSDR		2018 HR 1.52 (diagnosis) in civilian workers at Camp Lejeune; HR 1.31 in Camp Lejeune Marines	Median exposure in civilian workers: TCE=1086ug/L-months; PCE=457ug/L-months.	Monotonic: Medium Exposure=OR 1.80 & High Exposure=OR 13.02 for combined TCE+PCE in Camp Lejeune civilian employees compared to Camp Pendleton. Medium Exposure=OR 5.34 & I		0 ?	Camp Lejeune civilian employees 1973-1985 & Marines 1975-1985. Survey to form retrospective cohort then nested case-controls conducted
Bove (b-mortality)		2024 aHR 1.44 (mortality) in civilian workers and aHR 1.21 (mortality) in military personnel at Camp Lejeune	Monthly median water system contamination: TCE=356ug/L; PCE=85ug/L; Vinyl Chloride=22ug/L	Monotonic in civilian employees: low (1-5 quarters)=HR 1.36, medium (6-22 quarters)=1.38,& high duration of exposure (23-53 quarters)=HR 1.68. Non monotonic in military personnel: low	>75% deaths occured at least 10 years after last exposure	Y	Camp Lejeune civilian employees 1973-1985 & Military personnel 1975-1985.
Bove (a-military)		2014 HR 1.35 (mortality) in residents of Camp Lejeune; HR 1.50 (mortality) in at least Low Exposure to TVOC	Mean TVOC=9605.1ug/L-months; Low Exposure=>1 to 4600ug/L-months; Medium Exposure=>4600 to 12250ug/L-months; High Exposure=>12250 to 64016ug/L-months	Monotonic: Low exposure=HR 1.42; Medium Exposure=HR 1.44; High Exposure=HR 1.54	10 years (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune military personnel 1975-1985
Bove (a-morbidity)		2024 aHR 1.12 (diagnosis) in civilian workers at Camp Lejeune	Monthly median water system contamination: TCE=356ug/L; PCE=85ug/L; Vinyl Chloride=22ug/L	Monotonic in civilian employees: high duration of exposure (22-53 quarters)=HR 1.70. Non monotonic in military personnel: low duration of exposure (1-6 quarters)=HR 1.12	analysis began >10 years after exposure	Y	Camp Lejeune civilian employees 1973-1985 & Military personnel 1975-1985.
TCE							
Vamvakas		1998 aOR 10.8 (diagnosis)	Not quantified but thought to be exposed to levels "several fold higher" than 50 ppm	Monotonic: Low exposure=OR 6.61, Medium exposure=OR 11.92, High exposure=OR 11.42	Mean latency 33 years in cases and 18 years in controls	N	German factory workers. Exposures assigned by job description and interviews but no sampling although positive dose response with estimated intensity of exposure
Henschler		1995 SIR 7.97 (diagnosis)/SMR 3.28 (mortality)	Not Quantified but suspected to be in excess of 100-200 mg/m^3 with mean duration of exposure of 214 months	Not reported	Average latency 28 years	Y	German cardboard factory workers. Exposures assigned by job description and interviews but no sampling
Zhao		2005 RR 4.9 (diagnosis) in highest exposure group with significant trend for intensity of exposure; RR 2.03 (mortality) in highest exposure group	Not Quantified	Monotonic (diagnosis): Medium exposure=RR 1.87, High exposure=RR 4.90 & Monotonic (mortality): Medium exposure=RR 1.43, High exposure=RR 2.03	10 and 20 years	Y	Rocketdyne Workers at Santa Susana Field Laboratory, CA
Bruning		2003 OR 2.47 (diagnosis)	Not quantified but thought to be exposed to levels greater than 50 ppm with peaks likely >200 ppm	Increased frequency of narcotic symptoms following TCE exposure (serving as a surrogate for high peak exposures) were associated with higher measures of association with daily symptoms	Lags up to 20+ years reported with majority of cases having first exposure >20 years prior	N	German factory workers. Exposures assigned by job description and interviews but no sampling.
Boice		2006 SMR 2.22 (mortality) in test stand workers	Not Quantified	Increased exposure as measured by years as test stand mechanic and number of engine flushes were associated with kidney cancer	6 months up to 10 years	N	Rocketdyne Workers. Exposures assigned by job assignment. Urothelial cancers analyzed as bladder cancer rather than kidney cancer.
Hansen		2013 aHRR 2.04 (diagnosis) for highest level of exposure	Urine TCA levels utilized to stratify degrees of exposure but no estimated exposure concentrations included.	No monotonic dose response although highest urine TCA levels demonstrated HRR=2.04	10 and 20 years	Y	Pooled analysis of multiple Nordic TCE exposed workers
Purdue		2017 OR 2.0 (diagnosis) for those with at least 6 hours of weekly exposure. OR 1.7 (diagnosis) for those with at least 1560 cumulative hours exposed.	Not Quantified	OR 2.0 (diagnosis) for those with at least 6 hours of weekly exposure. OR 1.7 (diagnosis) for those with at least 1560 cumulative hours exposed.	5 and 15 years	?	US Kidney Cancer Study. Exposures assigned by job description.
Pesch		2000 OR up to 1.8 in females and up to 1.3 in males (diagnosis)	Not Quantified	No consistent dose response	Not reported	N	German occupational TCE exposures. Exposures assigned by job exposure matrix.
Andrew		2022 OR 1.78 (diagnosis) for 50th-75th percentile exposure	50th-75th percentile=>0 to 27.6 ug/L	No monotonic dose response although 50-75th percentile median TCE exposure with elevated risk of kidney cancer	0, 5, 10, and 15 years	?	New Hampshire TCE contaminated water supply
Buhagen		2016 SIR 1.7 (diagnosis)	Not Quantified	No dose response analysis performed	Not reported	?	Norwegian railroad workers
Charbotel		2006 aOR 1.64 (diagnosis); Low exposure aOR 1.42 (diagnosis). significant trend for cumulative dose.	Low exposure=1-150 ppm x years. Median cumulative exposure in cases=30 ppm.	Cumulative dose=peak with monotonic dose-response: Low/Medium=No peak=aOR 1.35; Low/Medium=Peak≤raOR 1.61; High=No peak≤raOR 1.76; High=Peak>aOR 2.73. Cumulative dose w	Not reported	?	French occupational TCE exposures. Study is basis for EPA's dose extrapolation in kidney cancer specific risk modeling of 5.49 x 10^-3 per ppm (inhalational) & 9.28 x 10^-3 per mg/kg/day.
Moore		2010 OR 1.63 (diagnosis); Low cumulative exposure OR 1.39 (diagnosis); Low average exposure OR 1.38 (diagnosis).	Low cumulative exposure=1.58 ppm x years with high cumulative exposure equal to or greater than this. Low average exposure=0.076 ppm with high average equal to or greater th	Monotonic: High cumulative TCE exposure=OR 2.02, high average intensity of TCE exposure=OR 2.34	20 year	N	Central and Eastern Europe kidney cancer cases
Blair		1998 RR 1.6 (mortality)	Not Quantified	No consistent dose response	Not reported	Y	Civilian employees at Hill Air Force Base, UT. Only relative exposures assessed based on job description
Bove (a-military)		2014 HR 1.50 (mortality) in at least Low Exposure to TCE	Mean TCE=5369.3ug/L-months; Low Exposure=>1 to 3300ug/L-months; Medium Exposure=>3100 to 7700ug/L-months; High Exposure=>7700 to 197455ug/L-months	Non-Monotonic: Low exposure=HR 1.54; Medium Exposure=HR 1.21; High Exposure=HR 1.52	10 (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune military personnel 1975-1985
Kelsh		2010 mRR 1.42	Not Quantified in meta-analysis	Monotonic dose response for cumulative exposure: Low=SRR 1.29; High=SRR 1.39.	Not reported	?	Meta-analysis
Anttila		1995 SIR 1.39 (diagnosis) only elevated in those followed for at least 10 years	Not Quantified	Not reported	No lag. Mean length of follow up 18 years	Y	Finnish TCE Production workers evaluated with urine TCE levels with median 48-90 umol/l although ranging up to >10000 umol/L
Karami		2012 mRR 1.32	Not Quantified	Not reported	Not reported	?	Meta-analysis
Morgan		1998 Exposed SMR 1.32 (mortality); High exposure SMR 1.78 (mortality)	Not quantified but highest exposure group >50 ppm	High exposure group=SMR 1.78; Peak medium and high vs low and no exposure=RR 1.89; High cumulative exposure=RR 1.59	Not reported	?	Aerospace workers at Hughes Aircraft, AZ. Only highest exposure group reported possible exposure range. Remainder are relative exposures. Urothelial cancers analyzed as bladder cancer rather then ki
ATSDR		2018 HR 1.31 (diagnosis) in Marines stationed at Camp Lejeune	Median exposure in Marines: TCE=110ug/L-months	Monotonic: Medium Exposure=OR 1.33 & High Exposure=OR 1.42 for in Marines stationed at Camp Lejeune compared to Camp Pendleton. Medium Exposure=OR 1.45 & High Exposure=1.57	No lag	?	Camp Lejeune civilian employees 1973-1985 & Marines 1975-1985. Survey to form retrospective cohort then nested case-controls conducted
Dosemeci		1999 OR 1.30 (diagnosis); OR 1.96 (diagnosis in women & OR 1.04 (diagnosis) in men	Not Quantified	Not reported	Not reported	N	Occupational organic solvent exposures in Minnesota
Scott		2011 mRR 1.27	Not Quantified	Highest exposure group=mRR 1.58	Not reported	?	Meta-analysis
Silver		2014 HR 1.24 (mortality)	Not Quantified	Not reported	10 year lag	?	Microelectric and business machine facility workers in New York state with TCE estimated using a semiquantitative exposure metric
Raaschou-Nielsen		2003 SIR 1.2 (diagnosis); High exposure SIR 1.4 (diagnosis)	Mean air concentration 318 mg/m^3 in the 1960s and 75 mg/m^3 in 1980s	Monotonic dose response for duration of employment: At least 5 years of employment=SIR 1.7; 1 to 5 years of employment=SIR 1.1	Up to at least 20 year lag. Mean follow up 17.6 years	Y	Danish TCE exposed workers. Urothelial cancers analyzed as kidney cancer with identical SIR when separated out.
Radican		2008 HR 1.18 (mortality)	Not Quantified	Not reported	Not reported	?	Civilian employees at Hill Air Force Base, UT. Only relative exposures assessed based on job description
Chang		2003 SMR 1.18 (mortality) in females but not males	Not Quantified	No consistent dose response	"Various latency" employed although details limited	?	Taiwanese electronics factory worker
Axelson		1994 SIR 1.16 (reported as SIR but actually cancer mortality)	Average exposure 20ppm or 110 mg/m^3 in air	Not reported	Not reported	?	Swedish TCE production workers evaluated with Urine-TCA levels with 81%<50mg/L
Vlaanderen		2013 HR 1.12 (diagnosis) only in 2nd tertile of exposure in females when stratified by sex	Not Quantified	Non-Monotonic: HR 1.12 (diagnosis) only in 2nd tertile of exposure in females when stratified by sex	No lag in primary analysis but sensitivity analyses up to 20 years	Y	Nordic Occupational Cancer (NOCCA) Study
Hansen		2001 SIR 1.1 (diagnosis)	Mean air TCE 65 mg/m^3 & median air TCE 19 mg/m^3	Not reported	Not reported	Y	Danish TCE exposed workers
PCE							
Pesch		2000 OR up to 2.2 in females and up to 1.4 in males (diagnosis)	Not Quantified	No consistent dose response	Not reported	N	German occupational TCE exposures as primary analysis with PCE also examined. Exposures assigned by job exposure matrix.
Anttila		1995 SIR 1.82 (diagnosis)	Not Quantified	Not reported	No lag. Mean length of follow up 18 years	Y	Finnish TCE Production workers also exposed to PCE
Callahan		2019 SMR 1.8 (mortality) in those who joined the union after 1960	Not Quantified	more elevated measures of association with increasing lag all with significant trend with max monotonic dose response in 20 year lagged analysis: High exposure=HR 24.4; Medium exposure	20 year	?	St. Louis MO dry cleaning union workers
Christensen		2013 OR 1.6 (diagnosis)	Not Quantified	"substantial" exposures=OR 3.1	5 year	Y	Occupational PCE exposures in Montreal
Bove (a-military)		2014 HR 1.55 (mortality) in at least Low Exposure to PCE	Mean PCE=402.6ug/L-months; Low Exposure=>1 to 155ug/L-months; Medium Exposure=>155 to 380ug/L-months; High Exposure=>380 to 8585ug/L-months	Non-Monotonic: Low exposure=HR 1.40; Medium Exposure=HR 1.82; High Exposure=HR 1.59	10 (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune military personnel 1975-1985
Ruder		2001 SMR 1.41 (mortality); SMR 1.73 (mortality) when restricted to PCE only exposures and without additional solvent exposures	Not Quantified	Not reported	Up to 20+ years	N	US dry cleaning workers. Urothelial cancers analyzed as bladder cancer rather then kidney cancer.
ATSDR		2018 OR 1.31 (diagnosis) in Marines stationed at Camp Lejeune	Median exposure in Marines: PCE=36ug/L-months	Monotonic: Medium Exposure=OR 1.28 & High Exposure=OR 1.79 for in Marines stationed at Camp Lejeune compared to Camp Pendleton. Medium Exposure=OR 1.43 & High Exposure=OR	No lag	?	Camp Lejeune civilian employees 1973-1985 & Marines 1975-1985. Survey to form retrospective cohort then nested case-controls conducted
Aschengrau		1993 OR 1.23 (mortality) in those with any exposure	Exposures not directly quantified but one representative exposed town had levels of 1.5-80 ug/L in medium/high use sites	Low exposure=OR 1.36	15 year latency period	?	Massachusets PCE contaminated water supplies
Purdue		2017 OR up to 1.2 (diagnosis)	Not Quantified	In the high intensity exposure only group, a significant trend with >1820 hours=OR 3.1.	Not reported	?	Chicago IL and Detroit MI kidney cancer cases with occupational exposures to PCE. Exposure intensity assigned by job description
Calvert		2011 SMR 1.14 (mortality); SMR 1.35 (mortality) when restricted to PCE only exposures and without additional solvent exposures	Not Quantified	Not reported	Up to 20+ years	N	US dry cleaning workers. Urothelial cancers analyzed as bladder cancer rather then kidney cancer.
Vlaanderen		2013 HR 1.11 (diagnosis) in first tertile of exposure in both sexes only elevated in males (HR 1.18) when stratified by sex	Not Quantified	Non-Monotonic: First tertile of cumulative exposure=HR 1.11 only elevated in males (HR 1.14) when stratified by sex	No lag in primary analysis but sensitivity analyses up to 20 years	Y	Nordic Occupational Cancer (NOCCA) Study
Benzene							
Greenland		1994 OR 4.29 (mortality)	Not Quantified	Max possible effect @ 97th percentile exposure=OR 1.9	2 year standard lag. Various analyses including one with 8 year latency.	?	MA transformer manufacturing workers with exposures assigned by job description.
Anttila		2015 OR 2.11 (diagnosis)	At factories: Background= >0.01 to 0.1 mg/m^3; Low= >0.1 to 0.3 mg/m^3; High= >0.3 to 1.6 mg/m^3	Monotonic for duration of exposure: <1 to 9 yr=OR 1.37, 10-19 yr=OR 2.27, at least 20 yr=OR 2.98. Monotonic for cumulative exposure: 0.001-0.16mg/m^3*yr=OR 1.69; 0.20-2.40mg/m^3*yr	Not reported	N	Oil refinery workers in Finland
Bove (b-civilian)		2014 Median or greater cumulative Benzene exposure=HR 1.82	Monthly median water system contamination: TCE=356.6ug/L; PCE=14.5ug/L; Vinyl Chloride=20.3ug/L; Benzene=4.1ug/L	Median or greater cumulative Benzene exposure=HR 1.82	10 (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune civilian employees 1973-1985
Hu		2002 aOR 1.8 (diagnosis) in males & aOR 1.3 (diagnosis) in females; positive dose response with increasing years of exposure	Not Quantified	Monotonic for duration of exposure: At least 6 yrs=aOR 2.1; 1 to 5 yrs=OR 1.1	Not reported	N	Canadian national cancer registry with occupational exposures to benzene. Exposure intensity assigned by job description
Bove (a-military)		2014 HR 1.48 (mortality) in at least Low Exposure to Benzene	Mean Benzene=104.7ug/L-months; Low Exposure=2 to 45ug/L-months; Medium Exposure=45 to 110ug/L-months; High Exposure=>110 to 601ug/L-months	Non-Monotonic: Low exposure=HR 1.31; Medium Exposure=HR 1.38; High Exposure=HR 1.36	10 (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune military personnel 1975-1985
Pesch		2000 OR up to 1.4 (diagnosis) depending on degree of exposure and method of estimating exposure	Not Quantified	No consistent dose response	Not reported	N	German occupational benzene exposures. Exposures assigned by job exposure matrix.
Wong		1987 SMR 1.4 (mortality) in those continuously exposed to benzene for at least 6 months	Not Quantified	Not reported	Not reported	Y	US chemical workers
Seyyedsalehi		2024 mRR 1.20	Not Quantified	No consistent dose response	Not reported	Y	Metaanalysis with overall pooled analysis including variable exposure assessments with many studies that don't explicitly identify benzene exposure
Gerin		1998 OR 1.2 (diagnosis) in low exposures; OR 1.3 (diagnosis) in medium/high exposures	Not Quantified	Monotonic for exposure level: Low=OR 1.2; Medium/High=OR 1.3.	"A reasonable period of latency"	Y	Kidney cancer cases in Montreal, CA with occupational benzene exposures. Intensity of exposure assigned by job description
Lynge		1997 SIR 1.3 (diagnosis) in males & SIR 1.2 (diagnosis) in females	Estimated 8 hr TWA 0.5-1.0 mg/m^3	Not reported	Not reported	N	Nordic service station workers. Renal pelvis cancers analyzed separately with SIR 2.0 in males.
Vinyl Chloride							
Hu		2002 aOR 2.0 (diagnosis) in males & aOR 1.6 (diagnosis) in females	Not Quantified	Monotonic for duration of exposure: At least 20 years=aOR 4.5; 1 to 19 years=aOR 1.7	Not reported	N	Canadian national cancer registry with occupational exposures to vinyl chloride. Exposure intensity assigned by job description
Bove (a-military)		2014 HR 1.55 (mortality) in at least Low Exposure to Vinyl Chloride	Mean Vinyl Chloride=458.9ug/L-months; Low Exposure=>1 to 205ug/L-months; Medium Exposure=>205 to 500ug/L-months; High Exposure=>500 to 2800ug/L-months	Non-Monotonic: Low exposure=HR 1.66; Medium Exposure=HR 1.61; High Exposure=HR 1.51	10 (primary); also 0, 15, and 20 year lag sensitivity analyses	?	Camp Lejeune military personnel 1975-1985
Mundt		2017 SMR 1.16 (mortality)	Not Quantified	Not reported	Not reported	N	US and canadian vinyl chloride occupational exposures

APPENDIX II – DR. HATTEN'S CV

CURRICULUM VITAE

NAME	Benjamin W. Hatten, MD MPH	DATE	12/06/2024

I. PRESENT POSITION AND ADDRESS

Academic Rank:	**Associate Professor**
Department:	**Section of Medical Toxicology,** **Department of Emergency Medicine &** **Division of Clinical Pharmacology and Toxicology,** **Department of Medicine** **University of Colorado School of Medicine**
Professional Addresses:	**University of Colorado School of Medicine** **Anschutz Medical Campus** **Department of Emergency Medicine** **Leprino Building, 7th Floor** **Campus Box B-215** **12401 E. 17th Avenue** **Aurora, CO 80045** **Office: 720-848-6867** **Fax: 720-848-7374** **Toxicology Associates** **26 W Dry Creek Circle** **Suite 815** **Littleton, CO 80120** **Office: 720-477-2500** **Fax: 720-598-0409** **Rocky Mountain Poison and Drug Safety** **777 Bannock Street** **MC 0180** **Denver, CO 80204** **Office: (303) 389-1100**
E-Mail Address:	**benjamin.hatten@cuanschutz.edu**

II. EDUCATION

UNDERGRADUATE	
1998 – 2002	Bachelor of Arts Hendrix College Conway, Arkansas
MEDICAL SCHOOL	
2002 – 2006	Doctor of Medicine University of Texas-Southwestern Medical School Dallas, Texas
GRADUATE EDUCATION	
2011- 2013	Master of Public Health Epidemiology and Biostatistics Track Oregon Master of Public Health Program Oregon Health and Science University Portland, Oregon
2023-Present 2023-2024	Master of Science in Palliative Care Interprofessional Graduate Certificate in Palliative Care University of Colorado-Anschutz Medical Campus Aurora, Colorado
INTERNSHIP/RESIDENCY:	
2006 – 2010	Residency in Emergency Medicine Denver Health Medical Center Denver, Colorado
FELLOWSHIP:	
2011- 2013	Medical Toxicology Fellowship Oregon Health and Science University Portland, Oregon

III. ACADEMIC APPOINTMENTS

2010-2011	Clinical Instructor of Emergency Medicine & Attending Physician Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado

2010-2011	Attending Physician Department of Emergency Medicine Denver Health Medical Center Denver, Colorado
2011-2013	Attending Physician Department of Emergency Medicine Portland Veterans Affairs Medical Center Portland, Oregon
2011-2014	Adjunct Assistant Professor of Emergency Medicine & Attending Physician Department of Emergency Medicine Oregon Health and Science University Portland, Oregon
2013-Present	Faculty University of Colorado School of Public Health Aurora, Colorado
2013-Present	Consulting Attending Physician Department of Emergency Medicine Children's Hospital of Colorado Aurora, Colorado
2013-Present	Consulting Attending Physician Department of Emergency Medicine Denver Health Medical Center Denver, Colorado
2013-Present	Attending Physician & Medical Toxicologist Rocky Mountain Poison and Drug Center Denver, Colorado
2013-2014	Clinical Instructor & Attending Physician Department of Emergency Medicine Department of Medicine University of Colorado School of Medicine Aurora, Colorado
2014-2021	Assistant Professor Department of Emergency Medicine Department of Medicine

University of Colorado School of Medicine
Aurora, Colorado

2021-Present — Associate Professor
Department of Emergency Medicine
Department of Medicine
University of Colorado School of Medicine
Aurora, Colorado

IV: NON-ACADEMIC PROFESSIONAL POSITIONS

POSITION

2008 — Physician
Nextcare Urgent Care
Aurora, Colorado

2008-2010 — Physician
Lone Tree Acute Care Center
Lone Tree, Colorado

2009 — Physician
ResortMed
Aspen, Colorado

2009-2011 — Emergency Physician
EmCare
Dallas, TX

2013-2014 — Emergency Physician
Emergency Physicians at Porter Hospitals
Englewood, Colorado

2013-Present — Medical Toxicologist
Toxicology Associates
Denver, Colorado

HOSPITAL PRIVILEGES

2009-2010 — Emergency Physician
St. Thomas More Hospital
Canon City, Colorado

2009-2011 — Emergency Physician
Prowers Medical Center
Lamar, Colorado

2013-2014	Emergency Physician Castle Rock Adventist Hospital Castle Rock, Colorado
2013-2014	Emergency Physician Parker Adventist Hospital Parker, Colorado
2013-2014	Emergency Physician Porter Adventist Hospital Denver, Colorado
2013-2014	Emergency Physician Littleton Adventist Hospital Littleton, Colorado
2013-Present	Medical Toxicology Consultant Porter Adventist Hospital Denver, Colorado
2013-Present	Medical Toxicology Consultant Littleton Adventist Hospital Littleton, Colorado
2013-Present	Medical Toxicology Consultant Swedish Medical Center Englewood, Colorado
2019-Present	Medical Toxicology Consultant UCHealth Highlands Ranch Hospital Highlands Ranch, Colorado

V. HONORS

2013	Alpha Omega Alpha Honor Society
2018	Fellow of the American College of Emergency Physicians (FACEP)
2020	Fellow of the American College of Medical Toxicology (FACMT)

VI. MEMBERSHIPS

2002 – Present	American Medical Association Positions Held: President, UT-SW Chapter Alternate Delegate, House of Delegates
2002-2006	Texas Medical Association Positions Held: President, UT-SW Chapter
2002-2006	Emergency Medicine Student's Association Positions Held: President, UT-SW Chapter Liaison, Emergency Medicine Residents' Association
2003 – Present	American College of Emergency Physicians Positions Held: Chair, Excited Delirium Task Force Member, Clinical Policies Committee Member, Academic Affairs Committee Member, Trauma and Injury Prevention Section Member, Toxicology Section
2003 – 2010	Emergency Medicine Residents' Association Positions Held: Representative, ACEP Clinical Policies Committee Representative, ACEP Academic Affairs Committee Liaison, UT-SW Emergency Medicine Interest Group
2006 – Present	Society for Academic Emergency Medicine
2006 – 2011 2013-Present	Colorado Chapter American College of Emergency Physicians
2006 – 2011	Colorado Medical Society
2011-2013	Oregon Chapter American College of Emergency Physicians

2011-2013	Oregon Medical Society
2011-Present	American Academy of Clinical Toxicology Positions Held: Representative, QT Prolongation ClinTox Collaborative Representative, Society of Toxicology Scientific Liaison Coalition
2011-Present	American College of Medical Toxicology
2022-2023	American Association for Emergency Psychiatry
2023-Present	Society of Toxicology Full Member Positions Held: Scientific Liaison Coalition, Working Group Co-Chair, Cannabis and Psychedelics AACT Representative

VII. SERVICE

ORGANIZATIONS

INTERNATIONAL

2016-present	Voting Group Member & Methodologist Clinical Toxicology Recommendations Collaboration: QT prolongation AACT/EAPCCT joint guideline

NATIONAL

2003	Alternate Delegate Texas Delegation House of Delegates American Medical Association Chicago, Illinois
2007 – 2008	Member Academic Affairs Committee American College of Emergency Physicians Irving, Texas
2008 – 2010 2014-Present	Member Clinical Policies Committee

	Procedural Sedation Subcommittee (2012-2014) TIA Subcommittee (2014-2016) Opioid Subcommittee Chair (2016-2020) Process Working Group Chair (2020-2023) Sedation Subcommittee (2021-2023) Marijuana Subcommittee Chair (2022-Present) Methods Publication Working Group Co-Chair (2023-Present) American College of Emergency Physicians Irving, Texas
2011-2012	Working Group Member Developing an Education Research Consortium Consensus Conference Society for Academic Emergency Medicine
2016-Present	QT Prolongation ClinTox Collaborative AACT Representative
2018-2019	Emergency Medicine Representative Antibiotics Guideline Panel American Dental Association
2018-2019	Emergency Medicine Representative Small Bowel Obstruction Appropriateness Criteria American College of Radiology
2018-2024	Emergency Medicine Representative Workup of Pleural Effusion or Pleural Disease Appropriateness Criteria American College of Radiology
2020-2021	Chair Excited Delirium Task Force American College of Emergency Physicians Irving, Texas
2021	Panel Member Best Practices for the Pre-hospital and Emergency Room Management of Agitation with Ketamine Food and Drug Administration/Center For Drug Evaluation and Research

(Virtual)

2022-Present
Scientific Liaison Coalition
Working Group Co-Chair, Cannabis & Psychedelics
AACT Representative
Society of Toxicology

2023-Present
Emergency Medicine Representative
Inflammatory Ear Disease
Appropriateness Criteria
American College of Radiology

2024
Organizer and Facilitator
EntheoTox: Navigating the Psychedelic Frontier
ACMT at NACCT Presymposium

REGIONAL

2010-2011
Annual Meeting Planning Committee Member
Western Regional Society of Academic Emergency Medicine
Co-Director Back Bowls Trivia

DEPARTMENTAL

2006 – 2007
2017-Present
Member
Wellness Committee
Residency in Emergency Medicine
Department of Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2008 – 2010
Member
Compliance Committee
Residency in Emergency Medicine
Department of Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2014-present
2018-present
Faculty Member
Secondary Reviewer
Case Review Committee
Department of Emergency Medicine
University of Colorado School of Medicine
Aurora, Colorado

2016	Member Zoning and Staffing RPM Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado
2016-2017	Member Incentive Revision Committee Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado
2017-Present	Member Clinical Competency Committee: PGY3 Denver Health Residency in Emergency Medicine Denver, Colorado
2017-Present	Member Art Chaos Ethics and Science (ACES) Residency in Emergency Medicine Department of Emergency Medicine Denver Health Medical Center Denver, Colorado
2018-Present	Medication Assisted Therapy (MAT) Provider Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado
2021	Member Staffing RPM Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado
2023	Member Tower 3 ED Staffing RPM Department of Emergency Medicine University of Colorado School of Medicine Aurora, Colorado
2023	Member Sick Call Policy Working Group Department of Emergency Medicine

University of Colorado School of Medicine
Aurora, Colorado

PUBLICATIONS/WORK PRODUCTS

QUALITY ASSURANCE PROJECTS

1. **Hatten B.** Emergency Department Thoracotomies: 2008-2009. Denver Health Residency in Emergency Medicine, Denver Health Medical Center. 2010.

CLINICAL PROTOCOLS

1. **Hatten B**. Methotrexate Policy. Oregon Poison Center, Oregon Health and Science University. 2012.

2. **Hatten B.** Lowenstein S. Syncope Pathway. Department of Emergency Medicine, University of Colorado School of Medicine. 2016

3. **Hatten B.** Lowenstein S. Low Back Pain Pathway. Department of Emergency Medicine, University of Colorado School of Medicine. 2016

ADMINISTRATION

1. Emergency Medicine Coding Matrix. 2015.

PUBLIC EVENTS

MEDIA INTERACTIONS

February 16, 2012	Arsenic in baby formula and energy foods Video Interview. KOIN Channel 6 News. Portland, Oregon.
February 1, 2017	A swig of hydrogen peroxide — promoted by alternative-health devotees — can kill you Print Interview Washington Post Washington, DC
February 3, 2017	Cleansing Benefits from Peroxide? Video Interview KCWY Channel 13 News Casper, WY
February 9, 2017	Drinking peroxide as 'natural' cure leads to dangerous blood clots Interview HealthDay New York, NY

February 20, 2017	Ingesting hydrogen peroxide can be fatal, researchers say Interview CNN Atlanta, GA

COMMUNITY OUTREACH

October 17, 2012	Designer Drugs Expert Panel Multnomah County Health Department Portland, Oregon
2017-2019	Exposure Protocol Denver Zoo Denver, CO

VIII. LICENSURE & CERTIFICATIONS

ACTIVE MEDICAL LICENSES

2007 - Present	Unrestricted Medical License State of Colorado License Number Available Upon Request Expires 04/30/2025
2011-Present	Unrestricted Medical License State of Oregon License Number Available Upon Request Expires 12/31/2025

CERTIFICATIONS

2007-Present	Controlled Substance Registration Certificate United States Department of Justice Drug Enforcement Administration License Number Available Upon Request Expires 10/31/2025
2011-Present	Emergency Medicine Board Certification American Board of Emergency Medicine License Number Available Upon Request Expires 12/2026
2014-Present	Medical Toxicology Board Certification American Board of Emergency Medicine License Number Available Upon Request Expires 12/2024

IX. INVENTIONS/PATENTS

N/A

X. REVIEW/REFEREE WORK

JOURNAL PEER REVIEWER

2013-Present	*Clinical Toxicology*
2013-Present	*Journal of Medical Toxicology*
2015-2016	*EM Practice*
2015-Present	*Academic Emergency Medicine*

GUIDELINE PEER REVIEWER

1. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline) A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP.
   J Am Coll Cardiol. 2011 Mar 23.
   Circulation. 2011 Mar 28.

2. ACOEM practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. Hegmann KT, Weiss MS, Bowden K, Branco F, DuBrueler K, Els C, Mandel S, McKinney DW, Miguel R, Mueller KL, Nadig RJ, Schaffer MI, Studt L, Talmage JB, Travis RL, Winters T, Thiese MS, Harris JS; American College of Occupational and Environmental Medicine.
   J Occup Environ Med. 2014 Dec;56(12):e143-59.

XI. INVITED PRESENTATIONS

<u>RESEARCH PRESENTATIONS</u>
INTERNATIONAL:

2014	Factors associated with prehospital naloxone use in the United States: 2010. Poster Presentation 34th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)

	Brussels, Belgium
2015	Toxic exposures in young children resulting in tracheal intubation Oral and Poster Presentations 35th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) St. Julian's, Malta
2015	Outcomes Following Nerve Agent Exposure Reported in the ToxIC Registry Poster Presentation 8th Mediterranean Emergency Medicine Congress Rome, Italy
2015	Outcomes Following Brodifacoum Exposure Reported in the ToxIC Registry (2010-2013) Oral Presentation 8th Mediterranean Emergency Medicine Congress Rome, Italy
2015	Outcomes Following Cyanide Exposure Reported in the ToxIC Registry (2010-2013) Oral Presentation 8th Mediterranean Emergency Medicine Congress Rome, Italy
2017	Plant and fungi exposures reported to the Toxicology Investigators Consortium (ToxIC) Poster Presentation North American Congress of Clinical Toxicology Vancouver, Canada
2018	Racial and ethnic characteristics in cases of intentional pharmaceutical exposure with concern for toxicity. Poster Presentation. 38th International Congress of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) Bucharest, Romania
2018	Kratom: natural painkiller or herbal enemy?

Poster Presentation.
38th International Congress of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT)
Bucharest, Romania

2019 — Back pain and muscle stiffness: a case of valbenazine-associated neuroleptic malignant syndrome
Poster Presentation.
39th International Congress of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT)
Naples, Italy

2022 — Incidence of rhabdomyolysis in single agent antimuscarinic exposures
Poster Presentation.
42nd International Congress of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT)
Tallin, Estonia

2024 — Pediatric alpha-2 agonist exposures in the ToxIC Registry
Poster Presentation.
44th International Congress of the European Association of Poison Centres and Clinical Toxicologists (EAPCCT)
Munich, Germany

NATIONAL PRESENTATIONS:

2004 — Can Midlevel Providers Perform Ultrasonography on Superficial Abscesses?
Poster Presentation
American College of Emergency Physicians Research Forum
San Francisco, California

2004 — A Prospective Study Comparing Standard Laryngoscopy to the Trachview Videoscope System for Orotracheal Intubation by Emergency Medicine Residents and Medical Students.
Poster Presentation

	American College of Emergency Physicians Research Forum San Francisco, California
2009	Assessing Residency Review Committee Compliance with an Electronic Survey Poster Presentation Society for Academic Emergency Medicine Annual Meeting New Orleans, Louisiana
2011	Change In Major Trauma Following A Law To Allow Expansion Of Alcohol Sales Poster Presentation Society for Academic Emergency Medicine Annual Meeting Boston, Massachusetts
2011	What Does Service Obligation" Or "Clinical Education" Mean?" Poster Presentation Council of Residency Directors Academic Assembly San Diego, California
2011	What Does Service Obligation" Or "Clinical Education" Mean?" Poster Presentation Society for Academic Emergency Medicine Annual Meeting Boston, Massachusetts
2012	The Spatial Epidemiology of Toxic Mushroom Ingestions in the United States: 2001-2011 Fellow-in-Training Research Symposium American College of Medical Toxicology Annual Meeting San Diego, California
2012	Characteristics of Salicylate Poisoned Patients with an Elevated INR Fellow-in-Training Research Symposium American College of Medical Toxicology Annual Meeting

San Diego, California

2012 Change in Major Trauma Following a Law to Allow Expansion of Alcohol Sales
Poster Presentation
American College of Medical Toxicology
Annual Meeting
San Diego, California

2012 Change in Ethanol Related Visits and Alcohol Withdrawal Visits to the Emergency Department Following a Law to Allow Expansion of Alcohol Sales
Poster Presentation
Society for Academic Emergency Medicine
Annual Meeting
Chicago, Illinois

2012 The epidemiology of mushroom ingestion calls to US poison control centers: 2001-2011.
Platform Presentation
North American Congress of Clinical Toxicology
Las Vegas, Nevada

2012 Arginine Hydrochloride overdose in an infant.
Poster Presentation
North American Congress of Clinical Toxicology
Las Vegas, Nevada

2012 Severe pediatric lead toxicity after ingestion of three intact rifle cartridges.
Poster Presentation
North American Congress of Clinical Toxicology
Las Vegas, Nevada

2012 First report of envenomation by the Great Lakes Bush Viper (Atheris nitschei).
Poster Presentation
North American Congress of Clinical Toxicology
Las Vegas, Nevada

2012 Cinnamania: 15 seconds of internet fame, 3 days in the ICU.
Poster Presentation

	North American Congress of Clinical Toxicology Las Vegas, Nevada
2012	Sensitivity and Positive Predictive Value of ICD-9-CM Codes for Alcohol-Related Diagnoses in the Emergency Department. Poster Presentation American College of Emergency Physicians Research Forum Denver, Colorado
2013	High Concentration Peroxide Ingestions: 2001-2011 Fellow-in-Training Research Symposium American College of Medical Toxicology Annual Meeting San Juan, Puerto Rico
2013	Major Bleeding Events in Salicylate Toxicity Poster Presentation American College of Medical Toxicology Annual Meeting San Juan, Puerto Rico
2013	Coral Snake Envenomations 2001-2011: Antivenin Use and Outcomes Oral Presentation Society for Academic Emergency Medicine Annual Meeting Atlanta, Georgia
2013	Outcomes following high concentration peroxide ingestions. Platform Presentation North American Congress of Clinical Toxicology Atlanta, Georgia
2013	Caustic injuries following high concentration peroxide ingestions: 2001-2011. Poster Presentation North American Congress of Clinical Toxicology Atlanta, Georgia
2013	Utility of CT and HBO therapy following high concentration peroxide ingestions: 2001-2011.

	Poster Presentation North American Congress of Clinical Toxicology Atlanta, Georgia
2013	What's the cost of better joints? move free advanced leading to hepatotoxicity. Poster Presentation North American Congress of Clinical Toxicology Atlanta, Georgia
2013	Predictors of Coagulopathy and Hemorrhage in Salicylate Toxicity Poster Presentation American College of Emergency Physicians Research Forum Seattle, Washington
2014	Aspirin and Fanconi syndrome: are there risk factors for its development? Poster Presentation North American Congress of Clinical Toxicology New Orleans, Louisiana
2015	Chemical Threat Agents Reported in the ToxIC Registry (2010-2013) Poster Presentation American College of Medical Toxicology Annual Meeting Clearwater Beach, Florida
2015	Medical Toxicology Consult Service at a Tertiary Care Children's Hospital Poster Presentation American College of Medical Toxicology Annual Meeting Clearwater Beach, Florida
2015	Prescription Opioid Exposures and Outcomes Among Older Adults Oral Presentation Society for Academic Emergency Medicine Annual Meeting San Diego, California

2015	QRS Widening Associated with Quetiapine Toxicity Poster Presentation North American Congress of Clinical Toxicology San Francisco, California
2017	Hydrogen Peroxide Exposures Reported to the Toxicology Investigators Consortium (ToxIC) Poster Presentation American College of Medical Toxicology Annual Meeting San Juan, Puerto Rico
2017	Muscimol and ibotenic acid containing mushrooms exposures: US National Poison Data System 2001-2011 Poster Presentation American College of Medical Toxicology Annual Meeting San Juan, Puerto Rico
2017	Parenteral Lidocaine to Treat Symptomatic Nephrolithiasis Poster Presentation Society for Academic Emergency Medicine Annual Meeting Orlando, Florida
2018	Monomethylhydrazine (MMH) Containing Mushroom Exposures: US National Poison Data System Poster Presentation American College of Medical Toxicology Annual Meeting Washington, District of Columbia
2018	ToxIC Extracorporeal Therapies SubRegistry: Update 2017 Poster Presentation American College of Medical Toxicology Annual Meeting Washington, District of Columbia
2019	Racial and Ethnic Patterns of Intentional Overdose

	Poster Presentation American College of Medical Toxicology Annual Meeting San Francisco, California
2019	Brief Asystole in a Four-Year-Old Following Ingestion of Cannabis Edibles Poster Presentation American College of Medical Toxicology Annual Meeting San Francisco, California
2019	The ToxIC Sodium Bicarbonate Subregistry: Treatment Recommendations and Clinical Outcomes on Behalf of the ToxIC Investigators Consortium (ToxIC) Poster Presentation North American Congress of Clinical Toxicology Nashville, Tennessee
2020	Applications of Machine Learning Within Clinical Toxicology: a Review Poster Presentation American College of Medical Toxicology Annual Meeting New York, New York (virtual)
2020	Outcomes of Hyperbaric Oxygen Treatment Following Hydrogen Peroxide Ingestion: A Systematic Review Poster Presentation North American Congress of Clinical Toxicology San Francisco, California (virtual)
2020	Timing of embolic phenomena after hydrogen peroxide exposure: a systematic review Oral and Poster Presentation North American Congress of Clinical Toxicology San Francisco, California (virtual)
2020	Evaluation of Parenteral Lidocaine for Nephrolithiasis-Induced Renal Colic in the ED Oral and Poster Presentation Society for Critical Care Medicine

(virtual)

2022 — The buprenorphine blues: severe precipitated opioid withdrawal requiring intubation in fentanyl users
Poster Presentation
North American Congress of Clinical Toxicology
San Francisco, California

REGIONAL PRESENTATIONS:

2011 — Change In Major Trauma Following A Law To Allow Expansion Of Alcohol Sales
Lightening Oral Abstract Presentation
Society for Academic Emergency Medicine
Western Regional Meeting
Keystone, Colorado

SPEAKING ENGAGEMENTS/INVITED PROFESSORSHIPS

INTERNATIONAL PRESENTATIONS:

2017 — Alpha-2 Agonist Toxicity
North American Congress of Clinical Toxicology
Vancouver, Canada

2023 — Latest Evidence in Toxicology
IV South Brazilian Congress of Adult and Pediatric Emergency Medicine
Porto Alegre, Brazil

2023 — Management of the Severely Agitated Patient
IV South Brazilian Congress of Adult and Pediatric Emergency Medicine
Porto Alegre, Brazil

2023 — Delirious or Dead: The History and Future of Hyperactive Delirium
North American Congress of Clinical Toxicology
Montreal, Canada

NATIONAL PRESENTATIONS:

2008 — Medical Student Symposium
Society for Academic Emergency Medicine
Annual Meeting
Washington, DC

2008 — Suture Workshop

	Keystone Nurse Practitioner Conference Keystone, Colorado
2012	What's New at Alpha-2 American College of Medical Toxicology National Teleconference
2013	Valproic Acid ERCAST/EMCrit
2014	Hill Criteria and Causal Analysis Western Fellows Portland, Oregon
2015	Physostigmine ERCAST/EMCrit
2015	The Mile High Club: The Effects of Marijuana Legalization in Colorado Society for Academic Emergency Medicine Annual Meeting San Diego, California
2017	Clinical Policy: Neuroimaging and Decision Making in Adult Mild Traumatic Brain Injury in the Acute Setting Rocky Mountain Trauma and Emergency Medicine Beaver Creek, Colorado
2021	Opioids Clinical Policy Review Initiation of Buprenorphine and Pain Management in the ED Implementation Workshop American College of Emergency Physicians Supported by a Substance Abuse and Mental Health Services Administration (SAMHSA) grant (Virtual)
2022	Hyperactive Delirium with Severe Agitation: Management in Emergency Settings American College of Emergency Physicians (Virtual:https://ecme.acep.org/diweb/catalog/item?id=10876545)
2022	Hyperactive Delirium with Severe Agitation:

Management in Emergency Settings
National Update on Behavioral Emergencies
Scottsdale, Arizona

2024 — Palliative Care & Psychedelics
North American Congress of Clinical Toxicology
Denver, CO

REGIONAL PRESENTATIONS:

2008 — Altered Mental Status
Denver Fire Department CME
Denver, Colorado

2008 — Suture Workshop
Emergency Medicine Interest Group
University of Colorado School of Medicine
Aurora, Colorado

2009 — Hyperthermia
Denver Fire Department CME
Denver, Colorado

2009 — Hypothermia
Denver Fire Department CME
Denver, Colorado

2009 — Environmental Emergencies
Denver Health Paramedic School
Denver, Colorado

2018 — Clinical Policies: Seizures & Asymptomatic Hypertension
Colorado Association of Physicians Assistants
Copper Mountain, Colorado

2021 — Opioid Use Guidelines
Colorado Association of Physicians Assistants
(Virtual)

XII. TEACHING RECORD

PRESENTATIONS
UNDERGRADUATE/MEDICAL STUDENTS

2009, 2010 — Wilderness Envenomations

SURG 6624
Introduction to Wilderness Medicine
University of Colorado School of Medicine
Aurora, Colorado

2010, 2011 — Outdoor Sporting Activities
SURG 8031
Wilderness Medicine
University of Colorado School of Medicine
Moab, Utah

2010, 2011 — Envenomations
SURG 8031
Wilderness Medicine
University of Colorado School of Medicine
Estes Park, Colorado

2018 — Medical Toxicology Evaluation
EMED 6620
History of Pharmacology and Toxicology
University of Colorado School of Medicine
Aurora, Colorado

GRADUATE STUDENTS/GRADUATE MEDICAL EDUCATION

2007 — Etomidate for RSI in Sepsis
Denver Health Residency in Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2008 — Wide Complex Tachycardia
Denver Health Residency in Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2008 — Heparin in ACS: A Question of Harm
Denver Health Residency in Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2009 — Morbidity and Mortality Conference
Denver Health Residency in Emergency Medicine
Denver Health Medical Center
Denver, Colorado

2009	Bad for Business: Public Policy and Injury Prevention Denver Health Residency in Emergency Medicine Denver Health Medical Center Denver, Colorado
2010	Envenomations Denver Health Residency in Emergency Medicine Denver Health Medical Center Denver, Colorado
2011-2012	Introduction to Toxicology Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2012	Morbidity and Mortality Conference Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2012	Rock n' Roll Toxicology Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2012	Agitated Patient Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2012	Severe Alcohol Withdrawal Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2013	Envenomations Emergency Medicine Residency Oregon Health and Science University Portland, Oregon
2014, 2019	Dermal Toxicology Environmental and Occupational Toxicology 6616 University of Colorado School of Public Health

	Aurora, Colorado
2014, 2019	Ophthalmic Toxicology Environmental and Occupational Toxicology 6616 University of Colorado School of Public Health Aurora, Colorado
2015-present (every 12-24 months)	Aspirin and NSAIDS Denver Health Residency in Emergency Medicine UCH-Advanced Practice Provider Group University of Colorado School of Medicine Denver, Colorado
2015-present (every 12-24 months)	Digoxin (Cardiac Glycosides) Denver Health Residency in Emergency Medicine University of Colorado School of Medicine Denver, Colorado
2015-present (every 12-24 months)	Seizures Denver Health Residency in Emergency Medicine University of Colorado School of Medicine Denver, Colorado
2015	Iron Denver Health Residency in Emergency Medicine University of Colorado School of Medicine Denver, Colorado
2017-2018	Note Writing Denver Health Residency in Emergency Medicine University of Colorado School of Medicine Denver, Colorado
2017-present (yearly)	Consultant Note Writing and Clinical Billing Medical Toxicology Fellowship Rocky Mountain Poison and Drug Safety Denver Health Medical Center
2017-present (yearly)	Aspirin and NSAIDS Medical Toxicology Fellowship Rocky Mountain Poison and Drug Safety Denver Health Medical Center
2017-present (yearly)	Causation

	Medical Toxicology Fellowship Rocky Mountain Poison and Drug Safety Denver Health Medical Center
2018	Introduction to Clinical Toxicology History of Pharmacology and Toxicology University of Colorado School of Medicine Aurora, Colorado

EDUCATION POSITIONS

2007-2011	Instructor SURG 8006 MSIV Emergency Medicine Rotation University of Colorado Hospital and Denver Health Medical Center University of Colorado School of Medicine Aurora, Colorado
2008-2011	Instructor IDPT 7031 MSIII Emergency Medicine Rotation University of Colorado School of Medicine Aurora, Colorado
2009-2011	Instructor SURG 6624 Introduction to Wilderness Medicine University of Colorado School of Medicine Aurora, Colorado
2009-2011	Instructor SURG 8031 Wilderness Medicine University of Colorado School of Medicine Aurora, Colorado
2010-2011 2013-2016	Preceptor IDPT 6000 Foundations of Doctoring University of Colorado School of Medicine Aurora, Colorado
2011-2014	Instructor ETOX 709X

	Medical Toxicology Oregon Health & Science University School of Medicine Portland, Oregon
2013-Present	Attending Physician/Instructor EMED 8004/8006 MSIV Emergency Medicine Rotations University of Colorado Hospital and Denver Health Medical Center University of Colorado School of Medicine Aurora, Colorado
2013-Present	Attending Physician/Instructor IDPT 7031 MSIII Emergency Medicine Rotation University of Colorado School of Medicine Aurora, Colorado
2013-Present	Attending Physician/Instructor EMED 8024 Medical Toxicology University of Colorado School of Medicine Denver, Colorado
2014-Present	Instructor/Lecturer Environmental and Occupational Toxicology 6616 University of Colorado School of Public Health Aurora, Colorado
2017-2018	Instructor EMED 6620 History of Pharmacology and Toxicology University of Colorado School of Medicine Aurora, Colorado
2017-Present	Developer and Lead Facilitator Forensic Curriculum Medical Toxicology Fellowship Rocky Mountain Poison and Drug Center Denver, Colorado

ATTENDING DUTIES

2010-2011	Supervision and bedside teaching of residents and

	medical students Emergency Department-9 hours/week Denver Health Medical Center Denver, Colorado
2010-2011	Supervision and bedside teaching of residents and medical students Emergency Department-14 hours/week University of Colorado Hospital Aurora, Colorado
2011-2013	Supervision and bedside teaching of residents and medical students Emergency Department-9 hours/week Oregon Health and Science University Portland, Oregon
2011-2013	Supervision and bedside teaching of residents and medical students Emergency Department- 5 hours/week Veteran's Administration Hospital Portland, Oregon
2013-present	Supervision and bedside teaching of residents and medical students Emergency Department- 14 hours/week University of Colorado Hospital Aurora, Colorado
2013-present	Supervision and bedside teaching of fellows Medical Toxicology Consults - 36 hours/week University of Colorado Hospital & Children's Hospital of Colorado Aurora, Colorado
2013-present	Supervision and bedside teaching of fellows Medical Toxicology Consults - 8 hours/week Denver Health Medical Center & Rocky Mountain Poison and Drug Center Denver, Colorado

ADMINISTRATIVE POSITIONS

2014-Present	Practicum Site Director Occupational Medicine Residency

University of Colorado School of Medicine
Denver, Colorado

2017-Present — Clinical Competency Committee: PGY3
Denver Health Residency in Emergency Medicine
Denver, Colorado

CURRICULUMS

1. **Hatten B.** Rosen's Reading Schedule, Denver Health Residency in Emergency Medicine, Denver Health Medical Center. 2008.

2. **Hatten B,** Houghland J, Moreira M. Elective Tracks, Denver Health Residency in Emergency Medicine, Denver Health Medical Center. 2008.

3. **Hatten B,** Cleveland N. Research Track, Denver Health Residency in Emergency Medicine, Denver Health Medical Center. 2008.

4. **Hatten B,** Armstrong L, Block B, Bookman K, Davis C, Jacquet G, Hurtado T. Wilderness Medicine Track. Denver Health Residency in Emergency Medicine, Denver Health Medical Center. 2008.

5. **Hatten B**. Forensic Curriculum. Medical Toxicology Fellowship. Rocky Mountain Poison and Drug Center. 2019.

XIII. GRANT SUPPORT

2012 — American College of Medical Toxicology
Spring Conference Travel Award
$500.

XIV. BIBLIOGRAPHY

* mentee

PUBLICATIONS

Original Research

1. Roppolo LP, White PF, **Hatten B**, Hynan LS, Pepe PE. Use of the TrachView videoscope as an adjunct to direct laryngoscopy for teaching orotracheal intubation. *Eur J Emerg Med.* 2012 Jun;19(3):196-9. PMID 21817909. doi: 10.1097/MEJ.0b013e328349edb2
2. Wang GS, Monte A, **Hatten** B, Brent J, Buchanan J, Heard KJ. Initiation of a medical toxicology consult service at a tertiary care children's hospital. *Clin Toxicol*. 2015 May;53(4):192-4. PMID: 25686099. doi: 10.3109/15563650.2015.1013196.
3. Beauchamp GA*, Hendrickson RG, **Hatten BW**; Toxicology Investigators Consortium (ToxIC). Endotracheal Intubation for Toxicologic Exposures: A

Retrospective Review of Toxicology Investigators Consortium (ToxIC) Cases. *J Emerg Med.* 2016 Oct;51(4):382-388.e11. PMID 27480352. doi: 10.1016/j.jemermed.2016.05.056

4. **Hatten BW**, French LK, Horowitz BZ, Hendrickson RG. Outcomes After High Concentration Peroxide Ingestions. *Ann Emerg Med.* 2017 Jun;69(6):726-736. PMID 28153539. doi: 10.1016/j.annemergmed.2016.11.022
5. **Hatten BW**, Hendrickson RG. Coagulopathy and bleeding associated with salicylate toxicity. *Clin Toxicol*. 2020 Jan;58(1):16-19. Epub 2019 Mar 22. PMID 30900477. doi: 10.1080/15563650.2019.1593432.
6. Berling I, **Hatten BW**, Hoffman RS, Othong R, Roberts DM, Mustafa RA, Yates C, Cormier M, Gosselin S. Guidelines for reporting case studies and series on drug-induced QT interval prolongation and its complications following acute overdose. *Clin Toxicol*. 2020 Jan;58(1):20-28. Epub 2019 Apr 24. PMID 31018700. doi: 10.1080/15563650.2019.1605077.
7. Levine M, Ruha AM, Wolk B, Caravati M, Brent J, Campleman S, Wax P; **ToxIC North American Snakebite Study Group.** When It Comes to Snakebites, Kids Are Little Adults: a Comparison of Adults and Children with Rattlesnake Bites. J Med Toxicol. 2020 Oct;16(4):444-451. Epub 2020 May 11. PMID: 32394223. doi: 10.1007/s13181-020-00776-6.
8. Greene S, Ruha AM, Campleman S, Brent J, Wax P; **ToxIC Snakebite Study Group.** Epidemiology, Clinical Features, and Management of Texas Coral Snake (Micrurus tener) Envenomations Reported to the North American Snakebite Registry. J Med Toxicol. 2021 Jan;17(1):51-56. Epub 2020 Aug 14. PMID: 32803694. doi: 10.1007/s13181-020-00806-3.

<u>Systematic Review/Evidence Based Practice Guideline/White Paper</u>

9. Howell JM, et al. **Oversight Committee Member**. Clinical policy: Critical issues in the evaluation and management of emergency department patients with suspected appendicitis. *Ann Emerg Med.* 2010 Jan;55(1):71-116. PMID 20116016. doi: 10.1016/j.annemergmed.2009.10.004
10. Diercks DB, et al. **Oversight Committee Member**. Clinical policy: critical issues in the evaluation of adult patients presenting to the emergency department with acute blunt abdominal trauma. *Ann Emerg Med.* 2011. 57(4):387-404. PMID 21453818. doi: 10.1016/j.annemergmed.2011.01.013
11. Fesmire FM, et al. **Oversight Committee Member**. Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. *Ann Emerg Med.* 2011. 57(6):628-652. PMID 21621092. doi: 10.1016/j.annemergmed.2011.01.020
12. Godwin SA, Burton JH, Gerardo CJ, **Hatten BW**, Mace SE, Silvers SM, Fesmire FM. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Procedural Sedation and Analgesia. Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med.* 2014; 63(2):247-258. PMID 24438649. doi: 10.1016/j.annemergmed.2013.10.015
13. Brown MD, et al. **Oversight Committee Member**. Clinical Policy: Use of

Intravenous Tissue Plasminogen Activator for the Management of Acute Ischemic Stroke in the Emergency Department. *Ann Emerg Med.* 2015 Sep;66(3):322-333. PMID 26304253. doi: 10.1016/j.annemergmed.2015.06.031
14. Hildreth AF, Takhar S, Clark MA, **Hatten B**. Evidence-Based Evaluation And Management Of Patients With Pharyngitis In The Emergency Department. *Emerg Med Pract.* 2015 Sep;17(9):1-16. PMID 26276908.
15. Mace SE, et al. **Oversight Committee Member**. Clinical Policy for Well-Appearing Infants and Children Younger Than 2 Years of Age Presenting to the Emergency Department With Fever. *Ann Emerg Med.* 2016 May;67(5):625-639. PMID 28395922. doi: 10.1016/j.annemergmed.2016.01.042
16. Lo BM, Carpenter CR, **Hatten BW**, Wright BJ, Brown MD. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Suspected Transient Ischemic Attack. Clinical Policy: Critical Issues in the Evaluation of Adult Patients With Suspected Transient Ischemic Attack in the Emergency Department. *Ann Emerg Med.* 2016 Sep;68(3):354-370. PMID 27568419. doi: 10.1016/j.annemergmed.2016.06.048
17. Wolf SJ, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Carbon Monoxide Poisoning. *Ann Emerg Med.* 2017 Jan;69(1):98-107. PMID 27993310. doi: 10.1016/j.annemergmed.2016.11.003
18. Hahn SA, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy. *Ann Emerg Med.* 2017 Feb;69(2):241-250. PMID 28126120. doi: 10.1016/j.annemergmed.2016.11.002
19. Nazarian DJ, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department. *Ann Emerg Med.* 2017 Apr;69(4):480-498. PMID 28335913. doi: 10.1016/j.annemergmed.2017.01.036
20. Promes SB, et al. **Oversight Committee Member**. Clinical Policy: Emergency Department Management of Patients Needing Reperfusion Therapy for Acute ST-Segment Elevation Myocardial Infarction. *Ann Emerg Med.* 2017 Nov;70(5):724-739. PMID 29056206. doi: 10.1016/j.annemergmed.2017.09.035
21. Tomaszewski, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Evaluation and Management of Emergency Department Patients With Suspected Non-ST-Elevation Acute Coronary Syndromes. *Ann Emerg Med.* 2018 Nov;72(5):e65-e106. PMID 30342745 doi: 10.1016/j.annemergmed.2018.07.045.
22. Godwin, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache. *Ann Emerg Med.* 2019 Oct;74(4):e41-e74. PMID 31543134. doi: 10.1016/j.annemergmed.2019.07.009.
23. Lockhart PB, Tampi MP, Abt E, Aminoshariae A, Durkin MJ, Fouad AF, Gopal P, **Hatten BW**, Kennedy E, Lang MS, Patton LL, Paumier T, Suda KJ, Pilcher L, Urquhart O, O'Brien KK, Carrasco-Labra A. Evidence-based clinical practice

guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: A report from the American Dental Association. *J Am Dent Assoc.* 2019 Nov;150(11):906-921.e12. PMID 31668170. doi: 10.1016/j.adaj.2019.08.020.

24. Tampi MP, Pilcher L, Urquhart O, Kennedy E, O'Brien KK, Lockhart PB, Abt E, Aminoshariae A, Durkin MJ, Fouad AF, Gopal P, **Hatten BW**, Lang MS, Patton LL, Paumier T, Suda KJ, Cho H, Carrasco-Labra A. Antibiotics for the urgent management of symptomatic irreversible pulpitis, symptomatic apical periodontitis, and localized acute apical abscess: Systematic review and meta-analysis-a report of the American Dental Association. *J Am Dent Assoc*. 2019 Dec;150(12):e179-e216. PMID 31761029. doi: 10.1016/j.adaj.2019.09.011.
25. Expert Panel on Gastrointestinal Imaging, Chang KJ, Marin D, Kim DH, Fowler KJ, Camacho MA, Cash BD, Garcia EM, **Hatten BW**, Kambadakone AR, Levy AD, Liu PS, Moreno C, Peterson CM, Pietryga JA, Siegel A, Weinstein S, Carucci LR. ACR Appropriateness Criteria® Suspected Small-Bowel Obstruction. *J Am Coll Radiol.* 2020 May;17(5S):S305-S314. PMID: 32370974. doi: 10.1016/j.jacr.2020.01.025.
26. **Hatten BW**, Cantrill SV, Dubin JS, Ketcham EM, Runde DP, Wall SP, Wolf SJ. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Opioids. Clinical Policy: Critical Issues Related to Opioids in Adult Patients Presenting to the Emergency Department. *Ann Emerg Med.* 2020 Sep;76(3):e13-e39. PMID: 32828340. doi: 10.1016/j.annemergmed.2020.06.049.
27. Smith, et al. **Oversight Committee Member.** Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia. *Ann Emerg Med.* 2021 Jan;77(1):e1-e57. PMID: 33349374. doi: 10.1016/j.annemergmed.2020.10.024.
28. **Hatten BW**, Bonney C*, Dunne RB, Hail SL, Ingalsbe GS*, Levy MK, Millin M, Myers BJ, Shih RD, Goodloe JM. ACEP Task Force Report on Hyperactive Delirium with Severe Agitation in Emergency Settings. American College of Emergency Physicians. June 23 2021. https://www.acep.org/globalassets/new-pdfs/education/acep-task-force-report-on-hyperactive-delirium-final.pdf
29. King A, Fee M*, McGlynn E, Marshall B, Akers KG, **Hatten B**. Timing of embolic phenomena after hydrogen peroxide exposure - a systematic review. *Clin Toxicol*. 2023 Jan;61(1):12-21. Epub 2022 Nov 28. PMID: 36440836. doi: 10.1080/15563650.2022.2144745.
30. Valente JH et al. **Oversight Committee Member.** Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Mild Traumatic Brain Injury. *Ann Emerg Med.* 2023 May;81(5):e63-e105. PMID: 37085214. doi: 10.1016/j.annemergmed.2023.01.014.
31. Diercks DB et al. **Oversight Committee Member.** Clinical Policy: Critical Issues in the Evaluation and Management of Emergency Department Patients With Suspected Appendicitis. *Ann Emerg Med.* 2023 Jun;81(6):e115-e152. PMID: 37210169. doi: 10.1016/j.annemergmed.2023.01.015.

32. Lo BM, et al. **Oversight Committee Member.** Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Acute Ischemic Stroke. *Ann Emerg Med.* 2023 Aug;82(2):e17-e64. PMID: 37479410. doi: 10.1016/j.annemergmed.2023.03.007.
33. Promes SB, et al. **Oversight Committee Member.** Use of high-sensitivity cardiac troponin in the emergency department: A policy resource and education paper (PREP) from the American College of Emergency Physicians. *J Am Coll Emerg Physicians Open*. 2023 Jul 6;4(4):e12999. PMID: 37426553. DOI: 10.1002/emp2.12999.
34. Thiessen MEW, Godwin SA, **Hatten BW**, Whittle JA, Haukoos JS, Diercks DB. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Severe Agitation. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Out-of-Hospital or Emergency Department Patients Presenting With Severe Agitation. *Ann Emerg Med.* 2024 Jan;83(1):e1-e30. PMID: 38105109. doi: 10.1016/j.annemergmed.2023.09.010.
35. Expert Panel on Thoracic Imaging; Morris MF, Henry TS, Raptis CA, Amin AN, Auffermann WF, **Hatten BW**, Kelly AM, Lai AR, Martin MD, Sandler KL, Sirajuddin A, Surasi DS, Chung JH. ACR Appropriateness Criteria® Workup of Pleural Effusion or Pleural Disease. *J Am Coll Radiol*. 2024 Jun;21(6S):S343-S352. PMID: 38823955. doi: 10.1016/j.jacr.2024.02.013.
36. Smith MD, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Seizures. *Ann Emerg Med.* 2024 Jul;84(1):e1-e12. PMID: 38906639. doi: 10.1016/j.annemergmed.2024.02.018.
37. Gerardo CJ, et al. **Oversight Committee Member**. Clinical Policy: Critical Issues in the Evaluation of Adult Patients Presenting to the Emergency Department With Acute Blunt Trauma. *Ann Emerg Med.* 2024 Oct;84(4):e25-e55. PMID: 39306386. doi: 10.1016/j.annemergmed.2024.05.027.
38. Lo BM, et al. **Oversight Committee Member**. Clinical Policy: Use of Thrombolytics for the Management of Acute Ischemic Stroke in the Emergency Department. *Ann Emerg Med.* 2024 Dec;84(6):e57-e86. PMID: 39578010. doi: 10.1016/j.annemergmed.2024.07.023.

Research Network

39. Love JS, et al. **Toxicology Investigators Consortium Study Group Member.** The Toxicology Investigators Consortium Case Registry-the 2021 Annual Report. *J Med Toxicol*. 2022 Oct;18(4):267-296. Epub 2022 Sep 7. PMID: 36070069. doi: 10.1007/s13181-022-00910-6.
40. Amaducci AM, et al. **Toxicology Investigators Consortium Study Group Member.** The Toxicology Investigators Consortium 2022 Annual Report. *J Med Toxicol*. 2023 Oct;19(4):313-340. PMID: 37644342. doi: 10.1007/s13181-023-00962-2.
41. Hughes A, et al. **Toxicology Investigators Consortium Study Group Member.** The Toxicology Investigators Consortium 2023 Annual Report. J Med Toxicol.

2024 Oct;20(4):350-380. PMID: 39256327. doi: 10.1007/s13181-024-01033.

Medical Education

42. Newgard CD, Beeson MS, Kessler CS, Kuppermann N, Linden JA, Gallahue F, Wolf S, **Hatten B**, Akhtar S, Dooley-Hash SL, Yarris L. Establishing an emergency medicine education research network. *Acad Emerg Med.* 2012 Dec;19(12):1468-75. PMID 23279253. doi: 10.1111/acem.12028

Case Reports

43. **Hatten B**, Browne V. Retinal detachment. *Emerg Med J*. 2011 Jan;28(1):83. PMID 20378746. doi: 10.1136/emj.2009.074344
44. **Hatten BW**, Bryant E. Bleeding scrotal arteriovenous malformation. *J Emerg Med*. 2012 Jun;42(6):e133-5. PMID 19682823. doi: 10.1016/j.jemermed.2009.05.026
45. Kusin S, Tesar J, **Hatten B**, Horowitz BZ, Hendrickson R, Leman R, Buser G. Severe methemoglobinemia and hemolytic anemia from aniline purchased as 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a recreational drug, on the Internet - Oregon, 2011. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep*. 2012 Feb 10;61:85-8. PMID 22318470. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6105a1.htm
46. **Hatten BW**, Bueso A*, French LK, Hendrickson RG, Horowitz BZ. Envenomation by the Great Lakes Bush Viper (Atheris nitschei). *Clin Toxicol.* 2013 Feb;51(2):114-6. PMID 23327286. doi: 10.3109/15563650.2012.763134
47. **Hatten BW**, Bueso A*, Craven P, Hendrickson RG, Horowitz BZ. Lead toxicity and endoscopic removal of ingested firearm cartridges. *Clin Toxicol.* 2013 Jun; 51(5):448-50. PMID 23641934. doi: 10.3109/15563650.2013.792114
48. Bonney CF*, **Hatten B**, Wang GS. Toxicity From Unintentional Pediatric Ingestion of a Performance-Enhancing Drug: A Case Report With Review of Clenbuterol Toxicity and Treatment. J Emerg Med. 2019 Sep 4. PMID 31493966. doi: 10.1016/j.jemermed.2019.06.016.

Editorials and Letters

49. **Hatten BW**, Hendrickson RG. Reply to "In response to "Coagulopathy and bleeding associated with salicylate toxicity" ". *Clin Toxicol*. 2019 Aug 15:1. PMID 31416368. doi: 10.1080/15563650.2019.1650939.

BOOKS

1. Brent J, Burkhart K, Dargan P, **Hatten B**, Megarbane B, Palmer R. Critical Care Toxicology, 2nd Edition. Springer. 2017.

BOOK CHAPTERS/NON-PEER REVIEWED PUBLICATIONS

1. Verification of Endotracheal Tube Placement. Policy Statement. American College of Emergency Physicians. 2009. Replaced by 2016 revision.
2. **Hatten B**, Krzyzaniak S*, Saghafi O*. Pharyngitis: Current Guidelines For

Emergency Clinicians. *EM Practice Guidelines Update.* 2011; 3(10)

3. Verification of Endotracheal Tube Placement. Policy Statement. American College of Emergency Physicians. 2016. https://www.acep.org/patient-care/policy-statements/verification-of-endotracheal-tube-placement/
4. Reversal of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) in the Presence of Major Life-Threatening Bleeding. *Ann Emerg Med*. 2017. Dec;70(6):944-945. PMID: 29157712. doi: 10.1016/j.annemergmed.2017.08.037.
5. **Hatten B**. Aspirin and Nonsteroidal Agents. In Walls, et al. Rosen's Emergency Medicine, 9th Edition. Elsevier. 2017.
6. **Hatten B**. Aspirin and Nonsteroidal Agents. In Walls, et al. Rosen's Emergency Medicine, 10th Edition. Elsevier. 2022.
7. Use of High-Sensitivity Cardiac Troponin in the Emergency Department. American College of Emergency Physicians. 2023. https://www.acep.org/patient-care/policy-statements/use-of-high-sensitivity-cardiac-troponin-in-the-emergency-department.

ABSTRACT PRESENTATIONS

1. Roppolo LP, Krackover B, Miller AH, **Hatten B**. Can Midlevel Providers Perform Ultrasonography on Superficial Abscesses? Poster Presentation. *Ann Emerg Med* 2004; 44(4):S83-S84.
2. Roppolo LP, Brockman CR, **Hatten B**, Hynan LS. A Prospective Study Comparing Standard Laryngoscopy to the Trachview Videoscope System for Orotracheal Intubation by Emergency Medicine Residents and Medical Students. Poster Presentation. *Ann Emerg Med* 2004; 44(4):S117-S118.
3. Vogel J, **Hatten B**, Druck J. Assessing Residency Review Committee Compliance with an Electronic Survey. Poster Presentation. *Acad Emerg Med* 2009; 16(4):S44-45.
4. **Hatten B**, Liao M, Byyny R, Caruso E, Haukoos J. Change In Major Trauma Following A Law To Allow Expansion Of Alcohol Sales. Poster Presentation. *Acad Emerg Med* 2011; 18(5):S61.
5. **Hatten B**, Sande M, Druck J. What Does "Service Obligation" or "Clinical Education" Mean? Poster Presentation. *Acad Emerg Med* 2011; 18(5):S59.
6. **Hatten B,** Liao M, Caruso E, Haukoos J. Change in Ethanol Related Visits and Alcohol Withdrawal Visits to the Emergency Department Following a Law to Allow Expansion of Alcohol Sales**.** Poster Presentation. *Acad Emerg Med* 2012; 19(4):S355.
7. **Hatten BW,** McKeown NJ, Hendrickson RG, Horowitz BZ. The spatial epidemiology of mushroom ingestion calls to US poison control centers: 2001-2011**.** Plenery Presentation. *Clin Toxicol* 2012; 50(7):574-575.
8. **Hatten BW,** McKeown NJ, Hendrickson RG. Arginine Hydrochloride overdose in an infant**.** Poster Presentation. *Clin Toxicol* 2012; 50(7):595-596.
9. **Hatten BW,** Bueso A*, Horowitz BZ. Severe pediatric lead toxicity after ingestion of three intact rifle cartridges**.** Poster Presentation. *Clin Toxicol* 2012; 50(7):597-598.

10. Williams BT, Schlein S, Caravati M, **Hatten B**. Botulism outbreak in a state prison from "pruno". Platform Presentation. *Clin Toxicol* 2012; 50(7):611-612.
11. **Hatten BW**, Bueso A*, French LK. First report of envenomation by the Great Lakes Bush Viper (Atheris nitschei). Poster Presentation. *Clin Toxicol* 2012; 50(7):648.
12. Kusin S, Pizarro-Osilla C, **Hatten BW**, Hendrickson RG, West PL. Cinnamania: 15 seconds of internet fame, 3 days in the ICU. Poster Presentation. *Clin Toxicol* 2012; 50(7):655.
13. **Hatten B**, Kaplan B, Kim H, Ginde A. Sensitivity and Positive Predictive Value of ICD-9-CM Codes for Alcohol-Related Diagnoses in the Emergency Department. Poster Presentation. *Ann Emerg Med* 2012; 60(4):S33.
14. **Hatten BW**, Lewis ME*, Russell JW*, Hendrickson RG. Major Bleeding Events in Salicylate Toxicity. Poster Presentation. *J Med Toxicol* 2013; 9(1) 82-105.
15. **Hatten BW**, Hendrickson RG, McKeown NJ, Freeman MD, Horowitz BZ. Coral Snake Envenomations 2001-2011: Antivenin Use and Outcomes. Oral Presentation. *Acad Emerg Med* 2013; 20(s1):S121.
16. **Hatten BW,** Keith LK, Hendrickson RG, Horowitz BZ. Outcomes following high concentration peroxide ingestions**.** Plenery Presentation. *Clin Toxicol* 2013; 51(7):582-583.
17. **Hatten BW,** Keith LK, Hendrickson RG, Horowitz BZ. Caustic injuries following high concentration peroxide ingestions: 2001-2011**.** Poster Presentation. *Clin Toxicol* 2013; 51(7):632.
18. **Hatten BW,** Keith LK, Hendrickson RG, Horowitz BZ. Utility of CT and HBO therapy following high concentration peroxide ingestions: 2001-2011**.** Poster Presentation. *Clin Toxicol* 2013; 51(7):632-633.
19. Lopez AM, Kusin S, **Hatten BW**, Horowitz BZ. What's the cost of better joints? move free advanced leading to hepatotoxicity**.** Poster Presentation. *Clin Toxicol* 2013; 51(7):638.
20. Kusin S, **Hatten BW,** Giffin S, Horowitz BZ. Participation and response times of U.S. poison centers in a nationwide chart review. Oral Presentation. *Clin Toxicol* 2013; 51(7):705-706.
21. Russell JW, **Hatten BW**, Lewis ME, Hendrickson RG. Predictors of Coagulopathy and Hemorrhage in Salicylate Toxicity. Poster Presentation. *Ann Emerg Med* 2013; 62(4):S123.
22. **Hatten BW,** Hendrickson RG, Daya M, Fu R, Newgard C. Factors associated with prehospital naloxone use in the United States: 2010. Poster Presentation. *Clin Toxicol* 2014; 52(4):295-443.
23. Lopez AM, **Hatten BW,** French LK, Hendrickson RG. Aspirin and Fanconi syndrome: are there risk factors for its development? Poster Presentation. *Clin Toxicol* 2014; 52(7):682-818.
24. **Hatten BW,** Brent JA, Wax PM. On behalf of the ACMT Toxicology Investigators Consortium (ToxIC). Chemical Threat Agents Reported in the ToxIC Registry (2010-2013). Poster Presentation. *J Med Toxicol* 2015; 11: 2-47.
25. Wang GS, Monte AA, **Hatten B**, Brent J, Buchanan J, Heard K. Medical

Toxicology Consult Service at a Tertiary Care Children's Hospital. Poster Presentation. *J Med Toxicol* 2015; 11: 2-47.

26. **Hatten BW**, West NA, Severtson SG, Green JL, Dart RC. Prescription Opioid Exposures and Outcomes Among Older Adults. Oral Presentation. *Acad Emerg Med* 2015; 22(s1):S138-139.
27. **Hatten BW,** Beauchamp GA*. On behalf of the ACMT Toxicology Investigators Consortium (ToxIC). Toxic exposures in young children resulting intracheal intubation. Oral & Poster Presentations. *Clin Toxicol* 2015; 53(4):299.
28. **Hatten BW**. QRS widening associated with quetiapine toxicity. Poster Presentation. *Clin Toxicol* 2015; 53(7):639-777.
29. **Hatten BW**. On behalf of the ACMT Toxicology Investigators Consortium (ToxIC). Hydrogen Peroxide Exposures Reported to the Toxicology Investigators Consortium (ToxIC). Poster Presentation. *J Med Toxicol* 2017 Mar; 13(1): 31.
30. Moss M*, Hendrickson R, **Hatten B**. Muscimol and ibotenic acid containing mushrooms exposures: US National Poison Data System 2001-2011. Poster Presentation. *J Med Toxicol* 2017 Mar; 13(1): 17-18.
31. Won KJ*, Jacknin G, **Hatten BW**. Parenteral Lidocaine to Treat Symptomatic Nephrolithiasis. Poster Presentation. *Acad Emerg Med* 2017 May;24 Suppl 1:S264.
32. Vo T*, Hendrickson R, **Hatten B**. Plant and fungi exposures reported to the Toxicology Investigators Consortium (ToxIC). Poster Presentation. *Clin Toxicol* 2017 Aug;55(7):689-868.
33. Prince G*, **Hatten B**. Monomethylhydrazine (MMH) Containing Mushroom Exposures: US National Poison Data System. Poster Presentation. *J Med Toxicol* 2018 14:3–67.
34. King J, Rege S, Murphy C, **Hatten B**, Haynes A. ToxIC Extracorporeal Therapies SubRegistry: Update 2017. Poster Presentation. *J Med Toxicol* 2018 14:3–67.
35. Camarena-Michel A*, **Hatten B**. Racial and ethnic characteristics in cases of intentional pharmaceutical exposure with concern for toxicity. Poster Presentation. *Clin Toxicol* 2018 June;56(6): 453–608
36. Noori M*, Hendrickson R, **Hatten B**. Kratom: natural painkiller or herbal enemy? Poster Presentation. *Clin Toxicol* 2018 June;56(6): 453–608
37. Camarena-Michel A*, **Hatten B**. Racial and Ethnic Patterns of Intentional Overdose. Poster Presentation. *J Med Toxicol.* 2019 Mar 1:53-107.
38. Halmo L*, Bonney C*, **Hatten B**. Brief Asystole in a Four-Year-Old Following Ingestion of Cannabis Edibles. Poster Presentation. *J Med Toxicol.* 2019 Mar 1:53-107.
39. Noori MR*, Boroughf WJ, **Hatten BW.** Back pain and muscle stiffness: a case of valbenazine-associated neuroleptic malignant syndrome. *Clin Toxicol.* Published online: 16 Apr 2019
40. Bruccoleri R, Davey M, Spyres M, Manini A, Dela Cruz M, Levine M, Carey J, **Hatten B**, Burns M. The ToxIC Sodium Bicarbonate Subregistry: Treatment Recommendations and Clinical Outcomes on Behalf of the ToxIC Investigators Consortium (ToxIC). *Clin Toxicol.* 2019 57:10, 870-1052.

41. Matsler N*, Hoyte C, **Hatten B.** Applications of Machine Learning Within Clinical Toxicology: a Review. *J Med Toxicol.* 2020 Feb 21 (online).
42. Fee M*, Akers K, Reed B, **Hatten B**, and King A. Outcomes of Hyperbaric Oxygen Treatment Following Hydrogen Peroxide Ingestion: A Systematic Review. *Clin Toxicol.* 2020 58:11, 1075-1280. (online)
43. Fee M*, Akers K, **Hatten B**, and King A. Timing of embolic phenomena after hydrogen peroxide exposure: a systematic review. *Clin Toxicol.* 2020 58:11, 1075-1280. (online)
44. Won KJ*, Jacknin G, Kiser T, Mueller S, Fish D, Maclaren R, **Hatten BW.** Evaluation of Parenteral Lidocaine for Nephrolithiasis-Induced Renal Colic in the ED. *Critical Care Medicine.* 2021. 49(1):1-50. (online)
45. Kaiser SK*, Kaplan S*, Nguyen H*, Hendrickson R, **Hatten B**. Incidence of rhabdomyolysis in single agent antimuscarinic exposures. *Clin Toxicol.* 2022 60:S1, 1-108.
46. Comstock G*, Kaiser S*, Boroughf W, **Hatten B**, Brent J. The buprenorphine blues: severe precipitated opioid withdrawal requiring intubation in fentanyl users. *Clin Toxicol.* 2022 60:S2, 1-162.
47. Han D*, Bonney C*, **Hatten B.** Pediatric alpha-2 agonist exposures in the ToxIC Registry. *Clin Toxicol.* 2024 62:S1, 1-135.

ABSTRACTS PUBLISHED:
(Abstract authored on previously published articles for the *Journal of Emergency Medicine* Abstract Section)

1. **Hatten B**. "Estimated Risk of Cancer Associated With Radiation Exposure From 64-Slice Computed Tomography Coronary Angiography: Einstein AJ, Henzlova MJ, Rajagopalan S. *JAMA* 2007; 298:317–23" J *Emerg Med*. 2007; 33(4): 443-444.
2. **Hatten B. "**What Causes Prolonged Fatigue after Infectious Mononucleosis: And Does It Tell Us Anything about Chronic Fatigue Syndrome? White PD. *J Infect Dis* 2007; 196:4–5." *J Emerg Med*. 2007; 33(4): 444-445.
3. **Hatten B.** "Risk Factors of Symptomatic Intracerebral Hemorrhage After tPA Therapy for Acute Stroke: Lansberg MG, Thijs VN, Bammer R, et al. *Stroke* 2007; 38:2275–8." *J Emerg Med*. 2007; 33(4): 446-447.
4. **Hatten B.** "Accuracy of Ultrasonography in Diagnosis of Testicular Rupture After Blunt Scrotal Trauma: Guichard G, El Ammari J, Del Coro C, et al. *Urology* 2008; 1:52–6." *J Emerg Med*. 2008; 35(1): 112.
5. **Hatten B. "**Who Survives from Out-of-Hospital Pulseless Electrical Activity? Vayrynen T, Kuisma M, Maatta T, Boyd J. *Resuscitation* 2008; 76:207–13." *J Emerg Med*. 2008; 35(1): 113.
6. **Hatten B.** "Early Risk of Stroke After Transient Ischemic Attack: A Review and Meta-Analysis: Wu CM, McLaughlin K, Lorenzetti DL, et al. *Arch Intern Med* 2007; 167:2417–22." *J Emerg Med*. 2008; 35(1): 115.

7. **Hatten B.** "Hyponatremia and Hypokalaemia During Intravenous Fluid Administration: Armon K, Riordan A, Playfor S, et al. *Arch Dis Child* 2008; 93:285–7." *J Emerg Med*. 2008; 35(3): 351.

DR. HATTEN'S TESTIMONY HISTORY

Benjamin Hatten MD MPH

Sworn Testimony

2021

Byers v Lawson 6th Judicial District: Wyoming (Campbell County)	Deposition and Trial

2022

Zantac Product Litigation The United States District Court for the Southern District of Florida MDL NO. 2924	Deposition

2023

Metcalf v Barretts Minerals Inc Los Angeles Superior Court	Deposition
Doig v Malcom and Flamingo Inc., d/b/a Blue Note Catering Denver District Court	Trial
Zantac Product Litigation Del. Super. Ct N22C-09-101 ZAN	Deposition

2024

Zantac Product Litigation Williams v Walgreen CO, et al Circuit Court of Cook County, Illinois	Deposition
Zantac Product Litigation Valadez v. GlaxoSmithKline LLC, et al. Circuit Court of Cook County, Illinois	Trial
Owners Insurance v. Keeton, et al US District Court, Colorado	Deposition
Zantac Product Litigation Joiner v. Walgreen Co., et al. Circuit Court of Cook County, Illinois	Trial
Zantac Product Litigation Kimbrow v. Walgreen Co., et al. Circuit Court of Cook County, Illinois	Trial
Zantac Product Litigation	Trial

Russell v BI
Alameda County, California

Zantac Product Litigation — Deposition
Mayor and City Council of Baltimore v.
GlaxoSmithKline LLC, et al.
Circuit Court for Baltimore City, Maryland

This list has been retrospectively constructed and is as complete as possible. It is conceivable that one or more episodes of testimony have been inadvertently left out.